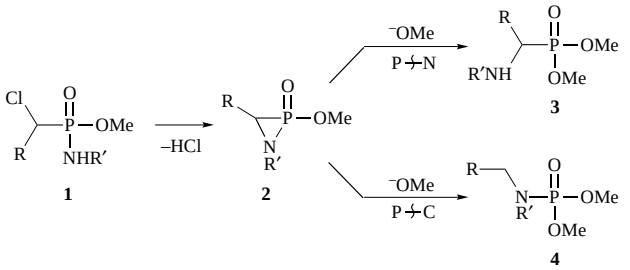
Alkoxide induced rearrangement of alkyl bromomethylphosphonamidates: steric influences on the direction of ring opening of the azaphosphiridine oxide intermediate

Martin J. P. Harger * and Ramesh Sreedharan-Menon

Department of Chemistry, The University, Leicester, UK LE1 7RH

Methyl *P*-bromomethyl-*N*-*tert*-butylphosphonamidate 10 (R = Me) rearranges with methoxide, giving dimethyl *tert*-butylaminomethylphosphonate 12 (R = R′ = Me) and dimethyl *N*-*tert*-butyl-*N*-methylphosphoramidate 13 (R = R′ = Me) in comparable amounts. These products are derived from the (postulated) azaphosphiridine oxide intermediate 11 (R = Me) by nucleophilic attack at phosphorus and cleavage of the P–N or P–C bond. Increased bulk in the alkyl group of the alkoxy ligand (R = methyl < cyclohexyl < *tert*-butyl < menthyl) or the alkoxide nucleophile (methoxide < *tert*-butoxide) increases P–N bond cleavage at the expense of P–C cleavage.

Azaphosphiridine oxides are the phosphorus analogues of α-lactams. They have not been isolated, unlike some other types of three-membered cyclic P=O compound,[1] but they have been postulated as reaction intermediates. In particular, the α-chlorophosphonamidates **1** react with methoxide to give two types of rearrangement product, the α-aminophosphonates **3** and the phosphoramidates **4** (Scheme 1).[2,3] This behaviour can



Scheme 1

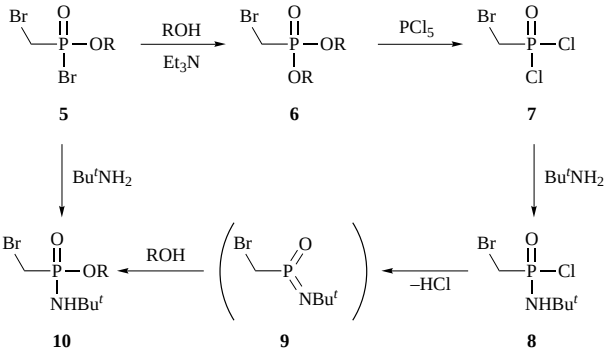
be rationalised in terms of an azaphosphiridine oxide intermediate **2**, resulting from the base-induced cyclisation of **1**. Nucleophilic attack at phosphorus and opening of the ring would then give **3** by cleavage of the P–N bond, and **4** by cleavage of the P–C bond. In accord with this, the relative amounts of the two types of product seems to depend on the relative abilities of the α-carbon and nitrogen atoms to depart from phosphorus as anions. Thus while **1** gives substantial amounts of both types of product when R = R′ = alkyl, the α-aminophosphonate (P–N bond cleavage) becomes dominant when R′ = Ph, and the phosphoramidate (P–C bond cleavage) when R = Ph.[2,3]

In a recent stereochemical study the behaviour of the menthyl α-bromomethylphosphonamidate **10** [R = menthyl (2-isopropyl-5-methylcyclohexyl)] was examined.[4] With methoxide this gave, as expected, the rearrangement products **12** and **13** (R = menthyl, R′ = Me) (see Scheme 3).[4] The ratio of the products, however, was 84:16 whereas previously the methyl α-chlorophosphonamidate [**10** (R = Me) with Cl in place of Br] had given the corresponding products [**12** and **13** (R = R′ = Me)] in a ratio of 38:62.[3] Such a pronounced difference is disquieting: if the azaphosphiridine oxide **11** is truly the only product-forming species (Scheme 3), the identity of the halogen (Br or Cl) in the substrate should be immaterial and the identity of the alkoxy ligand (menthoxy or methoxy) would not obviously be of much consequence either. We hoped that a study using substrates **10** with different alkoxy ligands would clarify the picture.

Results and discussion

Substrates

The preparation of suitable substrates **10** proved somewhat troublesome. For the methyl and cyclohexyl compounds, treatment of $BrCH_2P(O)Br_2$ (prepared from CH_2Br_2 and PBr_3–$AlBr_3$)[5] with the alcohol and Et_3N gave the alkyl phosphonobromidate **5** (R = Me or cyclohexyl), but some further reaction to form the dialkyl phosphonate **6** could not be avoided, especially with cyclohexanol. The impure phosphonobromidate was then treated with *tert*-butylamine and the required alkyl α-bromophosphonamidate **10** (R = Me or cyclohexyl) isolated by chromatography. A different approach was required for the *tert*-butyl compound **10** (R = Bu^t), making use of the ability of a phosphonamidic halide (*e.g.* **8**) to undergo substitution by an elimination–addition mechanism (Scheme 2).[6] This would



Scheme 2

generate a transient three-coordinate P^V intermediate (*e.g.* **9**) able to react even with a nucleophile as poor as *tert*-butyl alcohol. Unfortunately, the selective replacement of just one of the halogens in the dibromide [$BrCH_2P(O)Br_2$] is not possible with *tert*-butylamine,[7] so the less reactive dichloride **7** had to be used instead. It was prepared by converting $BrCH_2P(O)Br_2$ into the dimethyl phosphonate **6** (R = Me)

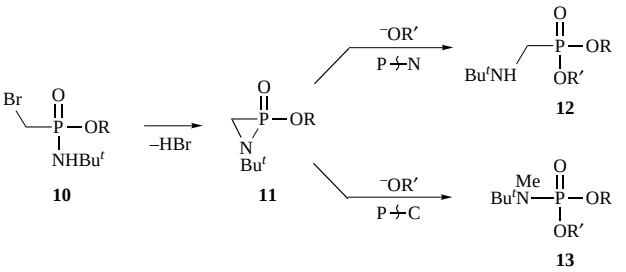
and heating this with PCl_5.† Controlled addition of *tert*-butylamine then gave the phosphonamidic chloride **8** (δ_P 29.5) with little if any disubstitution [δ_P 14.7 (3%) in the reaction mixture may have been due to some $BrCH_2P(O)(NHBu^t)_2$]. The phosphonamidic chloride reacted rapidly with $KOBu^t$ in *tert*-butyl alcohol to give the *tert*-butyl α-bromophosphonamidate **10** (R = Bu^t) although, because of the high basicity of *tert*-butoxide, further reaction of **10** (see below) competed with its formation and the yield was not good (29% after chromatography). By contrast, with NaOMe in methanol the phosphonamidic chloride **8** was converted cleanly into the methyl α-bromophosphonamidate **10** (R = Me). Unlike the menthyl compound **10** (R = menthyl),[4] the new α-bromophosphonamidates have only one chiral centre, so they do not exist as diastereoisomers.

Reactions of α-bromophosphonamidates

The methyl α-bromophosphonamidate **10** (R = Me) gave, as expected, the α-aminophosphonate **12** (R = R′ = Me) and the phosphoramidate **13** (R = R′ = Me) when treated with methoxide [$PhCH_2N^+Me_3$ ^-OMe (1.5 equiv.) in 9:1 THF–MeOH at room temperature; initial concentration 0.2 mol dm^{-3}]. The ratio of the products, as measured by ^{31}P NMR spectroscopy (δ_P 28.8 and 11.8), was 43:57. Previously, using the α-chloro analogue [**10** (R = Me) with Cl in place of Br], the same products were obtained in a ratio of 38:62.‡,[3] If the reactions proceed by initial base-induced cyclisation (elimination of HBr or HCl), the azaphosphiridine oxide intermediate **11** (R = Me) will be the same for both, and the final product ratios should be identical. They are not, but the discrepancy is small. Also, the conditions for the chloride [6.7:1 THF–MeOH at 50 °C][3] were not exactly the same as for the bromide. On balance it seems likely that the identity of the halogen in the substrate has no influence on the outcome of the reaction.

The effect of changing the alkoxy ligand in the α-bromophosphonamidate was seen when the cyclohexyl and *tert*-butyl compounds **10** (R = cyclohexyl or Bu^t) were examined. These also gave mixtures of the corresponding α-aminophosphonate **12** (R′ = Me) and phosphoramidate **13** (R′ = Me) with methoxide, but the product ratios were substantially different from those for the methyl compound (Table 1). Thus the nature of the alkoxy ligand in the azaphosphiridine oxide **11** is clearly of considerable importance. In particular, it seems that a bulky alkoxy group encourages cleavage of the P–N bond and/or discourages cleavage of the P–C bond. Moreover, it is not just a matter of whether the alkyl group in the alkoxy ligand is primary, secondary or tertiary; cyclohexyl and menthyl are both secondary but the substrate with R = menthyl gives more of the P–N bond cleavage product than does the substrate with R = cyclohexyl, or even that with R = *tert*-butyl. Presumably it is the isopropyl substituent at C-2 that is responsible for the effective bulk of the menthyl group.

To see if bulk in the nucleophile also influences the fate of the azaphosphiridine oxide intermediate, the reactions of the new α-bromophosphonamidates were repeated using potassium



Scheme 3

Table 1

	Product ratio **12** (P–N cleavage):**13** (P–C cleavage)[a]	
Substrate	With methoxide	With *tert*-butoxide
10 (R = Me)	43:57[b]	77:23[f]
10 (R = C_6H_{11})	57:43[c]	92:8[g]
10 (R = Bu^t)	68:32[d]	97:3[h]
10 (R = menthyl)	84:16[e]	

[a] Product ratios relate to peak areas in ^{31}P NMR spectra of quenched reaction mixtures. [b] δ_P 28.8 and 11.8. [c] δ_P 26.9 and 9.6. [d] δ_P 24.2 and 5.9. [e] δ_P 27.1, 26.8 (diastereoisomers) and 10.4, 9.3 (diastereoisomers). Ratio from ref. 4. [f] δ_P 23.8 and 5.9. [g] δ_P 21.9 and 3.6. [h] δ_P 19.0. Minor product not detected by ^{31}P NMR spectroscopy; ratio deduced from ^1H NMR spectrum of reaction mixture after work-up.

tert-butoxide [$KOBu^t$ (1.5 equiv.) in 9:1 THF–Bu^tOH at room temperature]. The rates of reaction were some 30 times greater than with methoxide [hence the problem encountered earlier in the preparation of **10** (R = Bu^t)], lending support to a mechanism in which the alkoxide acts as a base in the rate-limiting step, not as a nucleophile. However, it is the ratios in which the products **12** (R′ = Bu^t) and **13** (R′ = Bu^t) were formed (Table 1) that is our real concern. These differ substantially from the product ratios with methoxide, and in each case the change is towards reduced P–C bond cleavage. As with the alkoxy ligand, bulk in the alkoxide nucleophile seems also to make P–N bond cleavage relatively more favourable. It is true that the *tert*-butoxide and methoxide reactions are not strictly comparable, since differences in solvent polarity (THF–Bu^tOH *vs.* THF–MeOH) and the alkoxide counter ion (K^+ *vs.* $PhCH_2N^+Me_3$) might influence the balance between P–C and P–N bond cleavage. However, for the two reactions that give rise to identical products, *i.e.* **10** (R = Bu^t) with methoxide and **10** (R = Me) with *tert*-butoxide, the product ratios differ relatively little, suggesting that any medium effect is probably quite small. That being so, the relatively large change seen, for any given substrate, in going from methoxide to *tert*-butoxide, is most probably the result of a steric effect.§

Mechanistic considerations

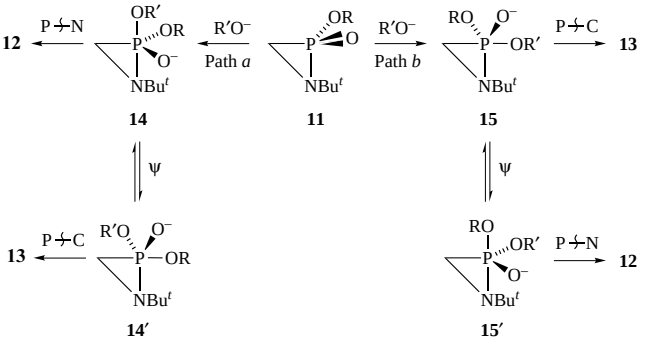
Substitution at a P=O centre generally involves formation of a trigonal-bipyramidal phosphorane intermediate, with the nucleophile initially occupying an apical position.[8] The trigonal bipyramid then collapses to product, directly or after one or more pseudorotations, by expulsion of the leaving group from

† Bromomethylphosphonic dichloride **7** is listed in two major reference works (G. M. Kosolapoff and L. Maier, *Organic Phosphorus Compounds*, Wiley Interscience, New York, 1972, vol. 4, p. 187; *Dictionary of Organophosphorus Compounds*, B-00475) but the data given, and references cited, seem actually to relate to the dibromide [$BrCH_2P(O)Br_2$]. The dichloride is mentioned in the patent literature but no details are given in *Chemical Abstracts* (*Chem. Abstr.*, 1978, **88**, P153546; 1980, **92**, P111683).

‡ The α-aminophosphonate product **12** (R = R′ = Me) suffers extensive demethylation [$>P(O)OMe + {}^-OMe \longrightarrow >P(O)O^- + MeOMe$] during the course of the reaction of the α-chloro substrate; the product ratio (38:62) relates to the situation after re-methylation with diazomethane (ref. 3). The α-bromo substrate reacts more readily, and demethylation of the product is less competitive; the product ratio (43:57) allows for the fact that *ca.* 10% of the product **12** (R = R′ = Me) (δ_P 28.8) was present in the demethylated state (δ_P 19.9).

§ The inclusion of a small amount of water (0.3 mol equiv.) in the reaction of the methyl substrate **10** (R = Me) with potassium *tert*-butoxide caused the formation of two new products, δ_P 20.3 and 7.6. These are thought to be the potassium salts of the acids **12** (R = Me, R′ = OH) and **13** (R = Me, R′ = OH) resulting from a competing reaction with hydroxide. The butoxide-derived products still indicated a 3:1 preference for P–N bond cleavage. By contrast, the hydroxide-derived products showed a 3:1 preference for P–C bond cleavage. Here, of course, the reaction medium is exactly the same for *tert*-butoxide and hydroxide, and the difference cannot possibly be due to a medium effect.

an apical position.[8] A three-membered ring will inevitably distort the geometry of the phosphorane:¶ to the extent that it still approximates to a trigonal bipyramid, the ring will be unable to span two equatorial positions (ideal bond angle 120°) and will have to be placed apical, equatorial (ideal bond angle 90°). In the case of the azaphosphiridine oxide **11**, the alkoxide nucleophile must therefore attack opposite the ring N atom to form the phosphorane **14**, or opposite the ring C atom to form **15** (Scheme 4); attack opposite the OR group is not



Scheme 4

possible, as it would place the ring diequatorial. The phosphoranes **14** and **15** can collapse directly to product **12** or **13** with cleavage of the apical P–N or P–C bond respectively. Alternatively, they can pseudorotate to give the new phosphoranes **14′** and **15′**; then it will be the other ring-bond (P–C or P–N) that is apical and breaks when the phosphorane collapses to product. Both types of product can therefore be formed by either pathway *a* or pathway *b* in Scheme 4.

Steric interactions will be at a minimum in the reaction of the methyl α-bromophosphonamidate **10** (R = Me) with methoxide, and it is here that the proportion of the P–C bond-cleavage product **13** is greatest (57%). Increased bulk in the substrate or the nucleophile diminishes P–C bond cleavage, either because pseudorotation to the new phosphorane **14′** becomes less important for reaction proceeding by pathway *a*, or because reaction by pathway *b* becomes less competitive. In the case of the nucleophile it may well be the latter: attack on the azaphosphiridine oxide **11** opposite the ring C atom must of necessity be adjacent to the N atom, and the *N-tert*-butyl group is likely to impede the approach of a bulky nucleophile.

As regards bulk in the substrate, it is known that in the reaction of the menthyl substrate with methoxide, the P–N bond is cleaved with inversion of configuration at phosphorus and the P–C bond with predominant retention.[4] This implies almost complete (99%) reaction by pathway *a*, with only a small part (one-twentieth) of the minor product (16%) arising from reaction by pathway *b* (P–C cleavage with inversion of configuration). The other substrates, with less bulky alkoxy ligands, give more P–C bond cleavage. If the stereochemistry of this extra P–C cleavage were known, we could tell whether it originates in phosphorane **14′** (retention of configuration) or phosphorane **15** (inversion of configuration). Unfortunately it is not known, and will not be easy to determine [our previous stereochemical study relied on having a chiral alkoxy ligand (menthoxy);[4] any suitable chiral alkoxy group will inevitably be quite bulky]. We therefore cannot properly explain why P–C bond cleavage is diminished by bulky alkoxy ligands, and a general observation must suffice. Phosphoranes are crowded molecules and steric interactions are potentially quite severe.[9] Of the two possible leaving groups in our phosphoranes (Scheme 4), one is bulky (NBu^t), the other (CH_2) is not. As the bond to phosphorus begins to break, there will be more immediate easing of the steric congestion if it is the bulky leaving group that departs. As the bulk of the alkoxy group OR (or OR′) increases, the benefit to be gained from shedding the more bulky leaving group will become more pronounced, so it is reasonable that P–N bond cleavage should become more important.

The fact that the relative yields of the two types of product are sensitive to steric effects may be of synthetic value. The α-aminophosphonates (P–N cleavage) are likely to be the more useful products, especially after dealkylation to the corresponding α-aminophosphonic acids, and it is these that are favoured by steric hindrance. Also, dealkylation of the α-aminophosphonate is especially easy with P–OBu^t groups:[10] it was not even possible to form salts by protonation of the amino group of **12** (R′ = Bu^t) without simultaneous acid-catalysed cleavage of the *O-tert*-butyl group [> P(O)OBu^t ⟶ > P(O)OH].

Experimental

Mps were determined using a Kofler hot-stage apparatus and are uncorrected. ^{1}H NMR spectra were recorded at 90 MHz on a Varian EM 390 spectrometer or (where indicated) at 300 MHz on a Bruker AM-300 (Me_4Si internal standard; coupling constants, *J*, given in Hz), and ^{31}P NMR spectra (^{1}H decoupled) were recorded at 36.2 MHz on a JEOL JNM-FX90Q spectrometer (positive chemical shifts downfield from external 85% H_3PO_4). Routine mass spectra were obtained in EI or (where indicated) CI mode on a VG 16-B or Kratos Concept spectrometer and high resolution spectra were recorded by the SERC Mass Spectrometry Service at Swansea. Potassium *tert*-butoxide was sublimed immediately before use. Solutions of benzyltrimethylammonium methoxide in methanol (40% w/w) were used as supplied. Methanol was distilled from its magnesium salt and THF from sodium–benzophenone. *tert*-Butyl alcohol was dried by prolonged storage over powdered 3 Å molecular sieves. Light petroleum refers to the fraction with bp 40–60 °C unless otherwise indicated and ether to diethyl ether. Dimethyl bromomethylphosphonate was prepared from bromomethylphosphonic dibromide[5] and MeOH–Et_3N; it had bp 110 °C (oven temp.) at 3 mmHg, $\delta_P(CDCl_3)$ 21.2, $\delta_H(CDCl_3)$ 3.79 (6 H, d, J_{PH} 11) and 3.27 (2 H, d, J_{PH} 9).

Methyl *P*-bromomethyl-*N*-*tert*-butylphosphonamidate 10 (R = Me)

A mixture of methanol (55 mg, 1.73 mmol) and triethylamine (174 mg, 1.73 mmol) in CH_2Cl_2 (3.5 ml) was added dropwise over 20 min to a stirred solution of bromomethylphosphonic dibromide[5] (509 mg, 1.69 mmol) in CH_2Cl_2 (4 ml) at *ca.* −25 °C. The mixture was allowed to warm to room temperature. After 40 min, it was cooled to 0 °C and *tert*-butylamine (273 mg, 3.7 mmol) in CH_2Cl_2 (2 ml) was added. After 50 min at room temperature, volatile material was removed and the residue was partitioned between ether and water. The organic portion was concentrated to give the crude product (273 mg, 66%). Chromatography [silica layer; ethyl acetate–light petroleum (2.3 : 1); R_f 0.16] followed by crystallisation from ether–light petroleum gave pure *methyl* P-*bromomethyl*-N-tert-*butylphosphonamidate* **10** (R = Me), mp 71.5–73 °C; $\delta_P(CDCl_3)$ 22.6; $\delta_H(CDCl_3$, 300 MHz) 3.74 (3 H, d, J_{PH} 11.1, OMe), 3.31 (2 H, ABP, δ_A 3.35, δ_B 3.26, J_{AB} 13.2, J_{AP} 9.6, J_{BP} 8.1, PCH_2Br), 2.78 (1 H, br d, J_{PH} 6, NH) and 1.35 (9 H, d, J_{PH} 0.7, NBu^t); *m/z* 230, 228 (M^+ − Me, 100%); *m/z* (CI) 263, 261 (M + NH_4^+, 20%), 246, 244 (M + H^+, 50), 230, 228 (M^+ − Me, 20), 183 (15), 166 (100) and 150 (25); ν_{max}(Nujol)/cm^{-1} 3220 (NH), 1240 and 1215 (P=O) (Found: C, 29.5; H, 6.0; N, 5.7. $C_6H_{15}BrNO_2P$ requires C, 29.5; H, 6.2; N, 5.7%).

¶ There are X-ray crystallographic data for one phosphorane with the phosphorus atom in a three-membered ring, albeit an unsaturated phosphirene ring (M. Ehle, O. Wagner, U. Bergsträsser and M. Regitz, *Tetrahedron Lett.*, 1990, **31**, 3429).

Cyclohexyl *P*-bromomethyl-*N*-*tert*-butylphosphonamidate 10 (R = C_6H_{11})

A mixture of cyclohexanol (335 mg, 3.35 mmol) and triethylamine (304 mg, 3.0 mmol) in CH_2Cl_2 (3 ml) was added to a stirred solution of bromomethylphosphonic dibromide[5] (903 mg, 3.0 mmol) in CH_2Cl_2 (3 ml) at room temperature. After 1 h, *tert*-butylamine (866 mg, 12 mmol) was added and the mixture was stirred for 10 min. All volatile material was removed and the residue was partitioned between ether and water. Chromatography of the organic portion [silica layer; ethyl acetate–light petroleum (1:1); R_f 0.20] followed by crystallisation from light petroleum afforded *cyclohexyl* P-*bromomethyl*-N-tert-*butylphosphonamidate* **10** (R = C_6H_{11}) (336 mg, 36%), mp 77–79 °C; $\delta_P(CDCl_3)$ 19.9; $\delta_H(CDCl_3$, 300 MHz) 4.50 (1 H, dtt, J_{PH} ~9, J_{HH} ~9 and 4.3, POCH), 3.33 (2 H, ABP, δ_A 3.36, δ_B 3.29, J_{AB} 13.1, J_{AP} 9.5, J_{BP} 7.7, PCH_2Br), 2.77 (1 H, br d, J_{PH} 7, NH), 2.08–1.93 (2 H, m), 1.87–1.73 (2 H, m), 1.68–1.51 (2 H, m), 1.49–1.22 (4 H, m,) and 1.39 (9 H, d, J_{PH} 0.6, NBu^t); *m/z* 298, 296 (M^+ − Me, 30%) and 216, 214 (M^+ − Me − C_6H_{10}, 100); *m/z* (CI) 314, 312 (M + H^+, 10%), 234 (60) and 74 (100); ν_{max}(Nujol)/cm^{-1} 3210 (NH), 1235 and 1215 (P=O) (Found: C, 42.4; H, 7.2; N, 4.6. $C_{11}H_{23}BrNO_2P$ requires C, 42.3; H, 7.4; N, 4.5%).

Bromomethylphosphonic dichloride 7

Dimethyl bromomethylphosphonate **6** (R = Me) (2.62 g, 12.9 mmol) was stirred while PCl_5 (6.36 g, 30.5 mmol) was added during 10 min. After 30 min the mixture was heated to 90 °C. Additional PCl_5 (0.55 g, 2.6 mmol) was added after 3.5 h and heating was continued for a further 30 min. Volatile material ($POCl_3$) was evaporated and the residue was distilled to give *bromomethylphosphonic dichloride* **7** (1.54 g, 56%), bp 68 °C (oven temp.) at 0.2 mmHg; $\delta_P(CDCl_3)$ 35.1; $\delta_H(CDCl_3)$ 3.95 (d, J_{PH} 6).

***tert*-Butyl *P*-bromomethyl-*N*-*tert*-butylphosphonamidate 10 (R = Bu^t)**

(a) A solution of bromomethylphosphonic dichloride **7** (1.27 g, 6.0 mmol) in CH_2Cl_2 (7 ml) was stirred at 0 °C while *tert*-butylamine (0.88 g, 12.0 mmol) in CH_2Cl_2 (6 ml) was added during 5 min. The mixture was allowed to warm to room temperature and after 30 min it was diluted with light petroleum (5 ml), filtered (to remove Bu^tNH_3Cl), and concentrated to give P-*bromomethyl*-N-tert-*butylphosphonamidic chloride* **8** (1.39 g, 93%), $\delta_P(CDCl_3)$ 29.5; $\delta_H(CDCl_3)$ 3.55 (2 H, d, J_{PH} 8), 3.45 (br, NH) and 1.41 (9 H, s).

(b) A small excess of KOBu^t (263 mg, 2.35 mmol) was added gradually, in small portions, to a stirred solution of the phosphonamidic chloride **8** (545 mg, 2.2 mmol) in *tert*-butyl alcohol (4 ml). The ^{31}P NMR spectrum indicated not only the desired product (δ_P 15.1, 45%) but also a by-product [δ_P 18.6, 30%; apparently the butoxide-induced rearrangement product **12** (R = R′ = Bu^t)] and some unchanged starting material (δ_P 28.8, 25%). More KOBu^t (77 mg, 0.7 mmol) was added in small portions to complete the reaction which was then quenched with NH_4Cl. Volatile material was evaporated and the residue was extracted with ether. The ether solution was washed with water containing just sufficient HCl to remove the by-product. Evaporation of the solvent gave the crude product (290 mg, 46%); chromatography [silica layer; EtOAc–light petroleum (1:1); R_f 0.18] and crystallisation from light petroleum afforded pure tert-*butyl* P-*bromomethyl*-N-tert-*butylphosphonamidate* **10** (R = Bu^t) (181 mg, 29%), mp 94–95 °C; $\delta_P(CDCl_3)$ 16.4; $\delta_H(CDCl_3$, 300 MHz) 3.24 (2 H, ABP, δ_A 3.27, δ_B 3.20, J_{AB} 12.9, J_{AP} 9.5, J_{BP} 7.5, PCH_2Br), 2.69 (1 H, br d, J_{PH} 5.7, NH; exchanges with D_2O), 1.53 (9 H, s, OBu^t) and 1.34 (9 H, d, J_{PH} 0.6, NBu^t); *m/z* 272, 270 (M^+ − Me, 30%) and 216, 214 (M^+ − Me − H_2C=CMe_2, 100); *m/z* (CI) 305, 303 (M + NH_4^+, 15%), 288, 286 (M + H^+, 40), 249, 247 (M + NH_4^+ − H_2C=CMe_2, 40) and 208 (100); ν_{max}(Nujol)/cm^{-1} 3220 (NH), 1240 and 1215 (P=O) (Found: C, 37.8; H, 7.3; N, 4.9. $C_9H_{21}BrNO_2P$ requires C, 37.8; H, 7.4; N, 4.9%).

Reactions of alkyl α-bromomethylphosphonamidates with alkoxides

The alkyl α-bromomethylphosphonamidate **10** (0.13 mmol) was dissolved in THF (0.45 ml) and mixed with either methanolic benzyltrimethylammonium methoxide (0.2 mmol, 0.1 ml) in THF (0.45 ml) or potassium *tert*-butoxide (22.5 mg, 0.2 mmol) in *tert*-butyl alcohol (0.1 ml) and THF (0.45 ml) at room temperature (reaction medium: 0.2 mol dm^{-3} alkoxide in 9:1 THF–alcohol). When the reaction was complete (2–3 h with methoxide; ≤5 min with *tert*-butoxide) the excess alkoxide was quenched (NH_4Cl) and the ratio of the rearrangement products was determined by ^{31}P NMR spectroscopy (peak areas) (Table 1). Volatile material was removed and the residue was dissolved in CH_2Cl_2 and washed with water. For the methoxide reactions, the aminomethylphosphonate product **12** was then extracted from the CH_2Cl_2 solution with water containing just sufficient HCl, leaving the phosphoramidate product **13** in the organic solution; the α-aminomethylphosphonate was recovered by basification of the aqueous solution and back-extraction into CH_2Cl_2. The organic portions were dried ($MgSO_4$), and evaporation of the solvent gave the two separated products. For the *tert*-butoxide reactions, because the P–OBu^t group was acid-labile, the products were separated by chromatography [rotating silica disc (chromatron); ethyl acetate, diluted initially with light petroleum (bp 60–80 °C); phosphoramidate eluted first]. The following were obtained (as oils).

From **10** (R = Me) with methoxide: *dimethyl* tert-*butylaminomethylphosphonate*[3] **12** (R = R′ = Me), $\delta_P(CDCl_3)$ 30.2; $\delta_H(CDCl_3)$ 3.80 (6 H, d, J_{PH} 11, OMe), 2.96 (2 H, d, J_{PH} 15, PCH_2N) and 1.09 (10 H, s, NBu^t and br s, NH); ν_{max}(film)/cm^{-1} 3300 (NH) and 1235 (P=O); and *dimethyl* N-tert-*butyl*-N-*methylphosphoramidate*[3] **13** (R = R′ = Me), $\delta_P(CDCl_3)$ 13.1; $\delta_H(CDCl_3)$ 3.66 (6 H, d, J_{PH} 11, OMe), 2.72 (3 H, d, J_{PH} 10, NMe) and 1.31 (9 H, s, NBu^t); ν_{max}(film)/cm^{-1} 1240 (P=O).

From **10** (R = Me) with *tert*-butoxide: tert-*butyl methyl* tert-*butylaminomethylphosphonate* **12** (R = Me, R′ = Bu^t), $\delta_P(CDCl_3)$ 25.3; $\delta_H(CDCl_3)$ 3.76 (3 H, d, J_{PH} 11, OMe), 2.88 (2 H, d, J_{PH} 15.5, PCH_2N), 1.63 (~2 H, br s, NH and water), 1.52 (9 H, s, OBu^t) and 1.08 (9 H, s, NBu^t); *m/z* (CI) 238 (M + H^+, 50%), 182 (M + H^+ − H_2C=CMe_2, 100), 166 (M^+ − H_2C=CMe_2 − Me, 10) and 86 (60) (Found: M + H^+, 238.157. $C_{10}H_{24}NO_3P$ requires *M* + H, 238.157); and tert-*butyl methyl* N-tert-*butyl*-N-*methylphosphoramidate* **13** (R = Me, R′ = Bu^t), $\delta_P(CDCl_3)$ 7.2; $\delta_H(CDCl_3$, 300 MHz) 3.60 (3 H, d, J_{PH} 11.5, OMe), 2.69 (3 H, d, J_{PH} 9.8, NMe), 1.47 (9 H, d, J_{PH} 0.3, OBu^t) and 1.30 (9 H, s, NBu^t); *m/z* (CI) 238 (M + H^+, 20), 222 (M^+ − Me, 5), 182 (M + H^+ − H_2C=CMe_2, 100), 166 (M^+ − Me − H_2C=CMe_2, 70) and 126 (M + H^+ − 2 H_2C=CMe_2, 35) (Found: M + H^+, 238.157. $C_{10}H_{24}NO_3P$ requires *M* + H, 238.157).

From **10** (R = Bu^t) with methoxide: a mixture of the same two products obtained above from **10** (R = Me) with *tert*-butoxide.

From **10** (R = Bu^t) with *tert*-butoxide: a mixture (separation not attempted) predominantly of *di*-tert-*butyl* tert-*butylaminomethylphosphonate* **12** (R = R′ = Bu^t), $\delta_P(CDCl_3)$ 20.1; $\delta_H(CDCl_3$, 300 MHz) 2.79 (2 H, d, J_{PH} 15.3, PCH_2N), 1.515 (19 H, s, OBu^t and br NH) and 1.07 (9 H, s, NBu^t); *m/z* 279 (M^+, 10%), 264 (M^+ − Me, 10), 208 (M^+ − Me − H_2C=CMe_2, 25), 166 (M^+ − Bu^t − H_2C=CMe_2, 25) and 152 (M^+ − Me − 2 H_2C=CMe_2, 100) (Found: M^+, 279.196. $C_{13}H_{30}NO_3P$ requires *M*, 279.196), with *di*-tert-*butyl* N-tert-*butyl*-N-*methylphosphoramidate* **13** (R = R′ = Bu^t), $\delta_P(CDCl_3)$ 0.9; $\delta_H(CDCl_3$, 300 MHz) 2.63 (3 H, d, J_{PH} 10.0, NMe), 1.46 (18 H, s, OBu^t) and 1.29 (9 H, s, NBu^t), as the minor component.

From **10** ($R = C_6H_{11}$) with methoxide: *cyclohexyl methyl* tert-*butylaminomethylphosphonate* **12** ($R = C_6H_{11}$, $R' = Me$), $\delta_P(CDCl_3)$ 28.2; $\delta_H(CDCl_3$, 300 MHz) 4.46 (1 H, dtt, J_{PH} ~9, J_{HH} ~9 and 5, POCH), 3.77 (3 H, d, J_{PH} 10.7, OMe), 2.92 (2 H, d, J_{PH} 15.1, PCH_2N), 2.03–1.88 (2 H, m), 1.83–1.68 (2 H, m), 1.61–1.01 (7 H, m; includes NH) and 1.08 (9 H, s, NBu^t); *m*/*z* 263 (M^+, 5%), 248 ($M^+ - Me$, 40) and 166 ($M^+ - Me - C_6H_{10}$, 100); picrate salt, mp 200–201.5 °C (decomp.) (from methanol); $\delta_P(CH_3OH)$ 17.3 (Found: C, 43.7; H, 5.8; N, 11.4. $C_{18}H_{29}N_4O_{10}P$ requires C, 43.9; H, 5.9; N, 11.4%); and *cyclohexyl methyl* N-tert-*butyl*-N-*methylphosphoramidate* **13** ($R = C_6H_{11}$, $R' = Me$), bp 99 °C (oven temp.) at 0.1 mmHg; $\delta_P(CDCl_3)$ 10.8; $\delta_H(CDCl_3$, 300 MHz) 4.315 (1 H, dtt, J_{PH} ~8, J_{HH} ~8 and 4, POCH), 3.63 (3 H, d, J_{PH} 11.3, OMe), 2.705 (3 H, d, J_{PH} 9.6, NMe), 2.02–1.87 (2 H, m), 1.81–1.67 (2 H, m), 1.61–1.16 [15 H; includes 1.31 (s, NBu^t)]; *m*/*z* 263 (M^+, 3%), 248 ($M^+ - Me$, 15) and 166 ($M^+ - Me - C_6H_{10}$, 100) (Found: M^+, 263.165. $C_{12}H_{26}NO_3P$ requires *M*, 263.165).

From **10** ($R = C_6H_{11}$) with *tert*-butoxide: tert-*butyl cyclohexyl* tert-*butylaminomethylphosphonate* **12** ($R = C_6H_{11}$, $R' = Bu^t$), $\delta_P(CDCl_3)$ 23.2; $\delta_H(CDCl_3$, 300 MHz) 4.44 (1 H, dtt, J_{PH} ~9, J_{HH} ~9 and 5, POCH), 2.83 (2 H, ABP, δ_A 2.84, δ_B 2.81, J_{AB} 13.8, J_{AP} 14.8, J_{BP} 15.8, PCH_2N), 2.05–1.91 (2 H, m), 1.82–1.68 (2 H, m), 1.62–1.10 [16 H; includes NH and 1.51 (s, OBu^t)] and 1.07 (9 H, s, NBu^t); *m*/*z* 305 (M^+, 5%), 290 ($M^+ - Me$, 25), 234 ($M^+ - Me - H_2C{=}CMe_2$, 60) and 152 ($M^+ - Me - H_2C{=}CMe_2 - C_6H_{10}$, 100) (Found: M^+, 305.212. $C_{15}H_{32}NO_3P$ requires *M*, 305.212); and tert-*butyl cyclohexyl* N-tert-*butyl*-N-*methylphosphoramidate* **13** ($R = C_6H_{11}$, $R' = Bu^t$), $\delta_P(CDCl_3)$ 4.9; $\delta_H(CDCl_3$, 300 MHz) 4.26 (1 H, dtt, J_{PH} ~8, J_{HH} ~8 and 4, POCH), 2.66 (3 H, d, J_{PH} 10.0, NMe), 2.01–1.85 (2 H, m), 1.79–1.64 (2 H, m), 1.60–1.16 [24 H; includes 1.46 (s, OBu^t) and 1.30 (s, NBu^t)]; *m*/*z* 305 (M^+, 2%), 290 ($M^+ - Me$, 7), 234 ($M^+ - Me - H_2C{=}CMe_2$, 30) and 152 ($M^+ - Me - H_2C{=}CMe_2 - C_6H_{10}$, 100) (Found: M^+, 305.212. $C_{15}H_{32}NO_3P$ requires *M*, 305.212).

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