Pergamon

Tetrahedron Letters, Vol. 36, No. 50, pp. 9201-9204, 1995
Elsevier Science Ltd
Printed in Great Britain
0040-4039/95 $9.50+0.00

0040-4039(95)01940-5

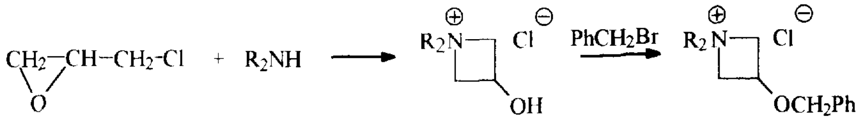
Ring-Opening of 3-Benzyloxyazetidinium Salts with Organophosphorus Nucleophiles. Application to the Synthesis of Polyfunctional Aminophosphonic Acids Analogues.

Jan Heliński, Zbigniew Skrzypczyński and Jan Michalski*

Centre of Molecular and Macromolecular Studies, Polish Academy of Sciences,
90-363 Łódź, Sienkiewicza 112, Poland

Abstract: Novel and efficient synthesis of polyfunctional γ- and δ-aminophosphonic acids derivatives via ring opening of 3-alkoxyazetidinium salts with phosphorus containing nucleophiles is described.

The potential importance of phosphonoaminoacids as enzyme inhibitors, chelating agents for metal anions and ligands in organometallic catalysts has encouraged us to find a convenient route towards the synthesis of γ- and δ-polyfunctional aminophosphonic acids. Thus, we came across the Gaertner reaction which allows remarkably easy access to 3-hydroxyazetidinium salts **1** from secondary amines and epichlorohydrine.[1,2] The 3-hydroxy group of the salt **1** can be efficiently protected by benzylation.[3]



1 2

Reference to the ring opening of salts **1** and **2** by nucleophiles is scarce.[4] Until now, however, the possibility of employing this reaction in the synthesis of organophosphorus compounds has not been explored. We report here on the synthesis of polyfunctional γ-aminophosphonic acids and γ-aminophosphines via ring opening of salts **2** by phosphorus nucleophiles. We also describe the synthesis of polyfunctional δ-aminophosphonic acids by ring opening of **2** by carbanions adjacent to the phosphoryl center.

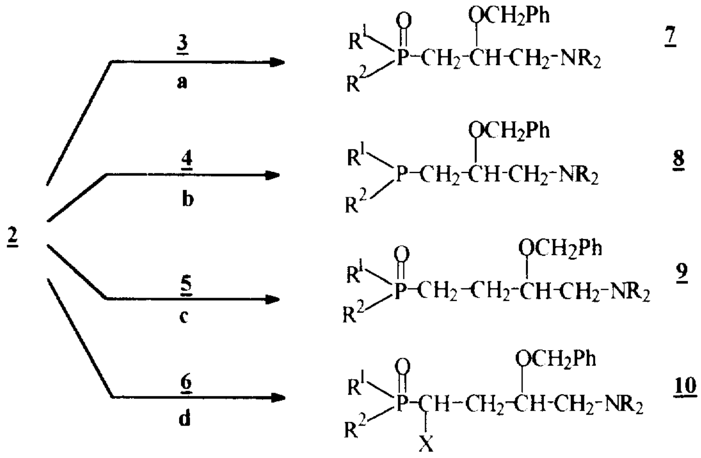
The nucleophiles used in this study can be divided into two major groups. The first are anionic species derived from hydrogen phosphine oxide type compounds $R^1R^2P(O)H$ **3** and hydrogen phosphines R^1R^2PH **4**. The second group is composed of carbanions with adjacent tetracoordinate phosphorus centers $CH_3P(O)R^1R^2$ **5** and $X\text{-}CH_2P(O)R^1R^2$ **6** where X represents additional carbanion stabilizing groups like COOR, CN, NO_2 and $P(O)R^1R^2$.

Typical examples of ring opening reactions of azetidinium salts **2a** (R=Et) by nucleophiles **3a** (R^1=R^2=OEt), **4a** (R^1=R^2=Ph), **5a** (R^1=R^2=OEt) and **6a** (R^1=R^2=OEt, X=COOEt) are shown in Scheme 1[5]

Yields of aminophosphonic esters **7-10** are also good in other cases (60-90%). Crude reaction products were purified by silica gel chromatography and their structures confirmed by NMR spectroscopy and elemental analysis.

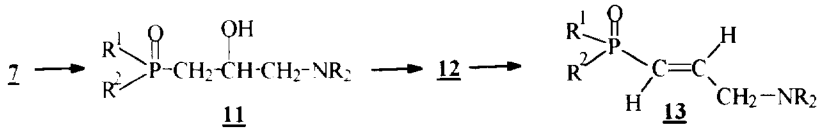
Catalytic hydrogenolysis of the benzyl ethers **7** led to compound **11** containing a free hydroxyl group. Alcohols **11** can be readily transformed into α,β-unsaturated phosphonic esters which are usually of E-configuration. This reactions proceed via the tosylate **12**.

* This paper is dedicated to Professor Ivar Ugi on the occasion of his 65th birthday.



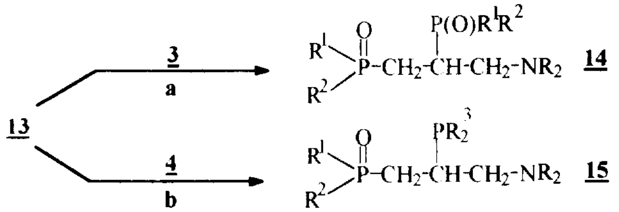
Scheme 1 Reactions a.b.c and d are exemplified by the synthesis of compounds: **7a**: **2a** + **3a,** NaH, DMF, 60°C 2 h (94%). **8a**: **2a** + **4a,** LDA, THF, -40°C, 2 h (87%) **9a**. **2a** + **5a,** LDA, THF, -40°C, 2 h (89%). **10a**: **2a** + **6a,** NaH, THF, 60°C, 2 h (90%)

Reaction of the alcohol **11** with tosyl chloride results in conversion to the tosylate **12** which undergoes elimination with potassium tert-butoxide in tert-butanol.These transformations are illustrated by the preparation of α,β-unsaturated compound **13a** (R=Et, R^1=R^2=OEt).



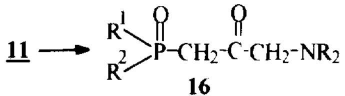
Scheme 2. Reagents and conditions: **11a: 7a** (R=Et, R^1=R^2=OEt), H_2, Pd/c, MeOH, room temp. 12 h (95%); **12a: 11a** (R=Et, R^1=R^2=OEt), TsCl, pyridine, 0°C, 12 h (90%); **13a:12a** (R=Et, R^1=R^2=OEt), Bu^tOK, Bu^tOH, 40°C, 6h (95%)

α,β-Unsaturated esters **13** are excellent substrates in the synthesis of systems **14** containing two phosphorus centers in β and γ-position in relation to the amino group (Scheme 3). For example, Michael addition of diethylphosphite **3a** (R^1=R^2=OEt) to the compound **13a** (R=Et, R^1=R^2=OEt) leads to the adduct **14a** (R=Et, R^1=R^2=OEt) (Reaction a). An analogous reaction with diphenylphosphine **4a** (R^1=R^2=Ph) gives the compound **15a** (R=Et, R^1=R^2=OEt, R^3=Ph) containing two phosphorus atoms of different coordination number (Reaction b).



Scheme 3. Reactions and conditions **14a** (reaction a) NaH, toluene, 60°C, 3 h (95%); **15a** (reaction b): NaH, toluene, 60°C, 3 h (91%)

The aminophosphonic esters **11** are readily oxidized into the corresponding ketones **16** .



16

Scheme 4. Reagents and conditions: **11a** (R=Et, R^1=R^2=OEt), Ac_2O, DMSO, -10°C, 3 h (90%).[8]

When aminophosphonic derivatives with a primary amino group are required N,N-dibenzylazetidinium salt **2** (R=CH_2Ph) can be used as a convenient substrate. All transformations described in this paper were performed under dry nitrogen and in the case of P^{III} compounds with deoxygenated solvents.

Chemical transformations presented in this paper illustrate the wide possibilities offered by ring opening of 3'-hydroxyazetidinium salts by a variety of nucleophiles. The strategy described here has significant potential in creating new polyfunctional organophosphorus structures especially those with chiral carbon and phosphorus centers.

Further studies on applications of this methodology are being carried out in our laboratory.

References and Notes

1. a) Gaertner, V.R. Tetrahedron Lett. **1964**, *3*, 141-146.
   b) Gaertner, V.R. Tetrahedron Lett. **1966**, *39*, 4691-4694.
   c) Gaertner, V.R. J.Org.Chem.,**1967**, *32*, 2972-2976.
2. Cromwell, N.H.; Philips, B. Chem.Rev. **1979**, *79*, 331-358.
3. Salt **2** (R=CH_2Ph) prepared by Gaerther's procedure[1] have been prepared from the salt **1** by alkylation with benzyl bromide in the presence of powdered potassium hydroxide and calcium hydride at 60°C. This reaction is completed within 3 h and affords **2** (R=CH_2Ph) in over 95% yield. After removal of solid phase the solution of **2** can be used for further transformations.
4. a) Gaertner, V.R. Tetrahedron Lett. **1967**, *4*, 343-347.
   b) Gaertner, V.R. J.Org.Chem. **1968**, *33*, 523-530.
   c) Gaertner, V.R. J.Het.Chem. **1969**, *6*, 273-277.
   d) Higgins, R.H.; Faircloth, W.J.; Baughman, R.G.; Eaton, Q.L. J.Org.Chem. **1994**, *59*, 2172-2178. Ring opening reactions of 1 have been reported by the above authors for the following nucleophiles: sodium methoxide and phenoxide, sodium tert-butyl mercaptide, diethylamine, N-methylaniline and potassium cyanide.
5. **7a**: silica gel (Kieselgel 60, 230-400 mesh), $CHCl_3$:MeOH, 30:1, Rf=0.45. ^{31}P NMR (80.961 MHz, $CDCl_3$) δ = 28.9. ^{1}H NMR (200.13 MHz, $CDCl_3$) δ = 0.52-0.55 (m, 6H, Et_2N); 0.84-0.95 [m, 6H, $(EtO)_2P(O)$]; 1,52-1.64 [m, 1H, $CH_2P(O)$]; 1,80-1.92 [m, 1H, $CH_2P(O)$]; 2.03-2.25 (m, 4H, Et_2N); 2.27-2.31 (m, 2H, CH_2N); 3.40-3.52 (m, 1H, CH); 3.55-3.70 [m, 4H, $(EtO)_2P(O)$]; 4.20-4.31 (2d, 2H, CH_2Ph); 6.70-7.1 (m, 5H, Ar). ^{13}C NMR (50.288 MHz, $CDCl_3$) δ = 11.83 (Et_2N); 16.09, 6.12, 16.17, 16.20 [$(EtO)_2P(O)$]; 29.11, 30.97 [$CH_2P(O)$]; 47,66 (CH_2N); 127.21, 127.65, 127.88, 127.97, 138.48 (Ar).
   8a: silica gel (Kieselgel 60, 230-400 mesh), $CHCl_3$:MeOH, 30:1, Rf=0.4. ^{31}P NMR (80.961 MHz, $CDCl_3$) δ = -12.7, ^{1}H NMR (200.13 MHz, $CDCl_3$) δ = 0.93 (t, 6H, Et_2N); 1.45-1.49 (m, 2H, CH_2P); 2.45-2.53 (m, 6H, Et_2NCH_2); 3.44-3.52 (m, 1H, CH), 4.31-4.52 (2d, 2H, CH_2Ph); 7.41-7.53, 7.62-7.73 (m, 15H, Ar); ^{13}C NMR (50.288 MHz, $CDCl_3$) δ = 12.45 (Et_2N); 30.32, 31.28 (CH_2P); 48.08 (Et_2N); 58.05, 58.16 (CH); 72.31 (CH_2Ph); 74.31 (CH_2N); 127.21-132.48 (Ar).
   9a: silica gel (Kieselgel 60, 230-400 mesh), $CHCl_3$: MeOH, 30:1, Rf=0.35. ^{31}P NMR (80.961 MHz, $CDCl_3$) δ = 27.2; ^{1}H NMR (200.13 MHz, $CDCl_3$) δ = 0.53-0.55 (m, 6H, Et_2N); 0.84-0.97 [m, 6H, $(EtO)_2P(O)$]; 1.47-1.55 [m, 1H, $CH_2P(O)$]; 1.68-1.72 [m, 1H, $CH_2P(O)$]; 1.83-1.97 (m, 2H, CH_2); 2.13-2.25 (m, 4H, Et_2N); 2.30-2.35 (m, 2H, CH_2N); 3.45-3.51 (m, 1H, CH); 3.57-3.75 [m, 4H,

$(EtO)_2P(O)]$, 4.31-4.38 (2d, 2H, CH_2Ph); 6.70-7.05 (m, 5H, Ar); ^{13}C NMR (50.288 MHz, $CDCl_3$) δ = 11.95 (Et_2N); 16.20, 16.25, 16.27, 16.30 $[(EtO)_2P(O)]$; 21.3, 21.54 (CH_2); 29.13, 31.05 ($CH_2P(O)$); 46.95 (Et_2N); 57.64 (CH); 61.25, 61.31, 61.35, 61.37 ($(EtO)_2P(O)$); 71.95 (CH_2Ph); 74.55 (CH_2N); 127.3-127.97 (Ar).

10a: silica gel (Kieselgel 60, 230-400 mesh), $CHCl_3$:MeOH, 30:1, Rf=0.31. ^{31}P NMR (80.961 MHz, $CDCl_3$) δ = 23.83, 24.13; ^{1}H NMR (200.13 MHz, $CDCl_3$) δ = 0.84-0.95 (m, 6H, Et_2N); 1.00-1.15 (m, 3H, COOEt); 1.17-1.29 [m, 6H, $(EtO)_2P(O)$]; 2.20-2.51 (m, 8H, CH_2, CH_2N, Et_2N); 3.07-3.29 [m, 1H, CHP(O)]; 3.38-3.45 [m, 1H, CH(OBn)]; 3.84-4.15 [m, 6H, $(EtO)_2P(O)$, COOEt]; 4.35-4.52 (m, 2H, CH_2Ph); 7.00-7.31 (m, 5H, Ar); ^{13}C NMR (50.288 MHz, $CDCl_3$) δ = 12.57, 12.60, 14.59, 14.69; 31.17, 31.23, 31.69, 31.74 [CHP(O)]; 41.47, 41.68 (CH_2); 48.43, 48.50, 57.92, 58.18, 61.78, 63.08, 63.17, 63.25, 63.34, 72.15, 72.67 (CH_2Ph); 126.53-129.32 (Ar); 169.79, 169.85, 170.06, 170.12 (C=O).

6. **11a**: silica gel (Kieselgel 60, 230-400 mesh), $CHCl_3$:MeOH, 10:1, Rf=0.3. ^{31}P NMR (80.961 MHz, $CDCl_3$) δ = 29.71. ^{1}H NMR (200.13 MHz, $CDCl_3$) δ = 0.54-0.56 (m, 6H, Et_2N); 0.90-0.97 [m, 6H, $(EtO)_2P(O)$]; 1.49-1.52 [m, 1H, $CH_2P(O)$]; 1.61-1.64 [m, 1H, $CH_2P(O)$]; 2.04-2.25 (m, 4H, Et_2N); 2.28-2.31 (m, 2H, CH_2N); 3.49-3.52 (m, 1, CH); 3.55-3.72 [m, 4H, $(EtO)_2P(O)$]. ^{13}C NMR (50.288 MHz, $CDCl_3$) δ = 12.34 (Et_2N); 18.29, 18.36 [$(EtO)_2P(O)$]; 32.93, 34.77 [$CH_2P(O)$]; 50.17 (Et_2N); 61.04, 61.23 [$(EtO)_2P(O)$]; 66.14 (CH_2N).

   12a: silica gel (Kieselgel 60, 230-400 mesh), $CHCl_3$:MeOH,l 20:1, Rf=0.45.

   13a: silica gel (Kieselgel 60, 230-400 mesh), $CHCl_3$:MeOH, 30:1, Rf=0.65. ^{31}P NMR (80.961 MHz, $CDCl_3$) δ = 17.85; ^{1}H NMR (200.13 MHz, $CDCl_3$) δ = 0.28-0.35 (t, 6H, Et_2N); 0.55-0.62 [t, 6H, $(EtO)_2P(O)$]; 1.70-1.82 (q, 4H, Et_2N); 2.49-2.52 (m, 2H, CH_2N); 3.28-3.45 [q, 4H, $(EtO)_2P(O)$]; 5.12-5.35 (m, 1H, CH); 5.90-6.12 (m, 1H, CH); ^{13}C NMR (50.288 MHz, $CDCl_3$) δ = 11.73 (Et_2N); 15.96, 16.04 ($(EtO)_2P(O)$); 47.01 (Et_2N), 55.38, 55.68 $(EtO)_2P(O)$; 61.18, 61.25 (NCH_2), 116.84, 119.32 [CHP(O)], 150.63 (CH).

7. **14a**: silica gel (Kieselgel 60, 230-400 mesh), $CHCl_3$:MeOH, 20:1, Rf=0.45. ^{31}P NMR (80.961 MHz, $CDCl_3$) δ = 30.61, 30.99, 31.87, 32.26. ^{1}H NMR (200.13 MHz, $CDCl_3$) δ = 0.61-0.73 (m, 6H, Et_2N); 0.94-1.15 [m, 12H, $(EtO)_2P(O)$]; 1.68-1.90 [m, 2H, $CH_2P(O)$], 1.90-2.15 (m, 1H, CH); 2.15-2.25 (m, 4H, Et_2N); 2.30-2.49 (m, 2H, CH_2N); 3.70-3.85 [m, 8H, $(EtO)_2P(O)$]. ^{13}C NMR (50.288 MHz, $CDCl_3$) δ = 11.05 (Et_3N); 16.23, 16.30 [$(EtO)_2P(O)$]; 22.12, 23.95 (CH); 29.49, 31.30 [$CH_2P(O)$]; 46.27 (Et_2N); 52.84, 52.91 (CH_2N); 61.28, 61.38, 61.47, 61.76, 61.84 [$(EtO)_2P(O)$].

   15a: silica gel (Kieselgel 60, 230-400 mesh), $CHCl_3$:MeOH, 20:1, Rf=0.35. ^{31}P NMR (80.961 MHz, $CDCl_3$) δ = 31.23, 31.34, 31.63, 31.75 [$(EtO)_2P(O)$]; 35.15, 35.32, 35.44, 35.73 [$Ph_2P(O)$]. ^{1}H NMR (200.13 MHz, $CDCl_3$) δ = 0.71-0.78 (m, H, Et_2N); 1.20-1.24 (m, 3H, [$EtO)_2P(O)$]; 1.27-1,31 [m, 3H, $[EtO)_2P(O)$], 1.89-2.05 [m, 2H, $CH_2P(O)$]; 2.37-2.45 (m, 4H, Et_2N), 2.75-2.82 (m, 2H, NCH_2); 3.00-3.18 (m, 1H, CH); 3.75-3.88 [m, 2H, $(EtO)_2P(O)$]; 4.00-4.15 [m, 2H, $(EtO)_2P(O)$]; 7.45-7.55 [m, 5H, Ar); 7.80-7.92 (m, 5H, Ar). ^{13}C NMR (50.288 MHz, $CDCl_3$) δ = 11.21, 16.92, 17.07, 17.79, 22.63, 24.49 $CH_2P(O)$]; 31.98, 32.93 [CHP(O)]; 46.30, 53.67, 62.03, 62.12, 62.21, 62.29, 77.06, 77.48, 77.89, 128.63-129.28, 131.32-132.83 (Ar).

8. **16a**: silica gel (Kieselgel 60, 230-400 mest), $CHCl_3$:MeOH, 30:1, Rf=0.25. ^{31}P NMR (80.961 MHz, $CHCl_3$) δ = 31.25; ^{1}H NMR (200.13 MHz, $CDCl_3$) δ = 0.55-0.57 (m, 6H, Et_2N); 0.91-0.99 (m, 6H, $(EtO)_2P(O)$); 1.49-1.53 (m, 2H, $CH_2P(O)$); 2.01-2.05 (m, 4H, Et_2N); 2.30-2.33 (m, 2H, CH_2N); 3.50-3.71 (m, 4H, $(EtO)_2P(O)$); ^{13}C NMR (50.288 MHz, $CDCl_3$) δ = 12.34 (Et_2N); 18.30, 18.36 ($(EtO)_2P(O)$); 35.93, 37.25 ($CH_2P(O)$); 50.21 (Et_2N), 61.04, 61.25 $(EtO)_2P(O)$); 68.18 (CH_2N); 170.6, 170.9 (C=O).

(*Received in UK* 5 *September* 1995; *revised* 11 *October* 1995; *accepted* 13 *October* 1995)