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Synthesis of *N*-Alkyl/Aryl-α/β-Aminoalkylphosphonic Acids from Organodichloroboranes and α/β-Azidoalkylphosphonates via Polyborophosphonates

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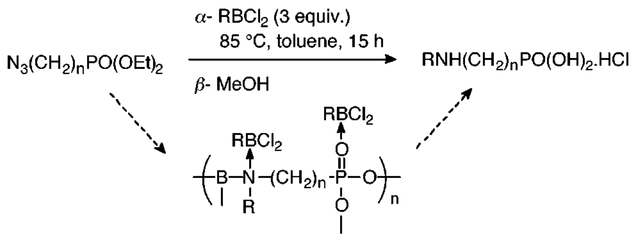
ABSTRACT



***N*-Alkyl/aryl-α- and β-aminoalkylphosphonic acids can be effectively prepared by reductive alkylation of azidoalkylphosphonates with organodichloroboranes. The reaction is accompanied by simultaneous dealkylation of the phosphonates occurring via polyborophosphonates.**

Aminoalkylphosphonic acids are probably the most important substitutes for the corresponding amino acids in biological systems. Acting as antagonists for amino acids, they inhibit enzymes involved in amino acid metabolism and thus affect the physiological activity of cells. These actions may be exerted as antibacterial, plant growth regulatory or neuromodulatory effects.[1]

α- and β-aminoalkylphosphonates have been synthesized by various routes.[2,3] However, their hydrolysis to corresponding free amino acids often requires harsh reaction conditions incompatible with many functional groups. For example, the hydrolysis conditions of the diethyl phosphonate

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(1) For reviews, see: (a) Drey, C. N. C. In *Chemistry and Biochemistry of the Amino Acids*; Barrett, G. C., Ed.; Chapman and Hall: London, 1985; pp 25−54. (b) Hiratake, J.; Oda, J. *Biosci. Biotechnol. Biochem.* **1997**, *61*, 211. (c) Kafarski, P.; Lejczak, B. *Phosphorus, Sulfur, Silicon* **1991**, *63*, 193. (d) Griffith, O. W. *Annu. Rev. Biochem.* **1986**, *55*, 855−878.

(2) Reviews: (a) *Enantioselective Synthesis of β-Amino Acids*; Juaristi, E., Ed.; Wiley-VCH: New York, 1996. (b) Cole, D. C. *Tetrahedron* **1994**, 50, 9517. (c) Kukhar, V. P.; Yu Svistunova, N.; Solodenko, V. A.; Soloshonok, V. A. *Russ. Chem. Rev.* **1993**, 62, 261. (d) Gubnitskaya, E. S.; Peresypkina, L. P.; Samarai, L. I. *Russ. Chem. Rev.* **1990**, 59, 807.

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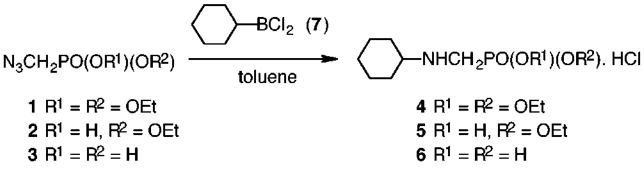
group require treatment with pure hydrochloric or hydrobromic acid for several hours.[4] Besides, *N*-alkyl/aryl-α- and *β*-aminoalkylphosphonic acids, which represent an interesting group of antimicrobial and antifungal agents,[1] are not effectively prepared by known methods.[5,6] The abilty to synthesize a variety of these bifunctional molecules from a common intermediate would greatly simplify the preparation of such derivatives.

In this paper, we wish to present a general synthesis leading to *N*-alkyl/aryl-α- and *β*-aminoalkylphosphonic acids based on reductive alkylation of α-and *β*-azidoalkylphosphonates with organodichloroboranes. The transformation is accompanied by simultaneous dealkylation of the phosphonates occurring via polyborophosphonates.

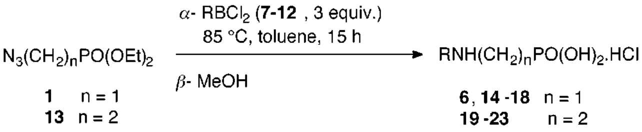
A useful method to prepare secondary amines is the reductive alkylation of organic azides with alkylboranes.[7] Unexpectedly, no reductive alkylation was observed when diethyl α-azidomethylphosphonate (**1**)[8] was heated with 1 equiv of cyclohexyldichloroborane (**7**)[9] for 4 h at 85 °C. Instead α-azidomethylphosphonic acid (**3**) was obtained (Scheme 1).[10] The use of 3 equiv of **7** gave *N*-cyclohexyl-α-aminomethylphosphonic acid (**6**) in excellent yield (95%) after 15 h at 85 °C. When less than 3 equiv of **7** was employed, for shorter reaction time or lower temperatures, mixtures of the compounds **1**−**6** in various amounts were obtained.

Scheme 1



The optimized conditions (3 equiv of borane, 15 h heating at 85 °C) were used for the synthesis of a series of *N*-alkyl-α-aminomethylphosphonic acids (Scheme 2 and Table 1).

Scheme 2



Alkyldichloroboranes **7**−**11** were reacted with azidoalkylphosphonates **1** and **13**[11] to yield the HCl salt of the corresponding *N*-alkyl-α- and *β*-aminoalkylphosphonic acids **6**, **14**−**17**, and **19**−**23** in excellent yields. With phenyldichloroborane (**12**), the reaction became more sluggish and the yield dropped off.

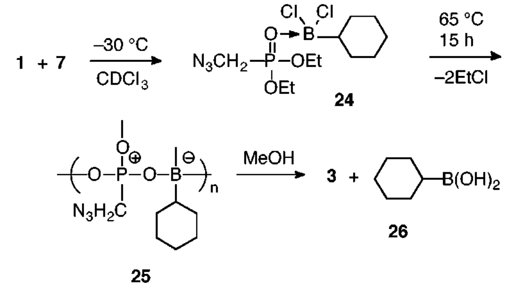
Table 1. Synthesis of N-Substituted α- and *β*-Aminophosphonic Acid Hydrochlorides[a,b]

$RBCl_2$, R =	product ($n = 1$)	yield[d] (%)	product ($n = 2$)	yield[d] (%)
cyclohexyl (**7**)	6	95	19	85
1-octyl (**8**)	14	98	20	83
1-hexyl (**9**)	15	98	21	85
2,3-dimethyl-1-butyl (**10**)	16	84	22	82
(1*R*,2*S*,3*R*,5*R*)-isopino-camphéyl (**11**)[c]	17	94	23	85[e]
phenyl (**12**)	18	42		

[a] See ref 9. [b] All compounds exhibited analytical and spectral data in accordance with the assigned structures. [c] Obtained from (+)-α-pinene. [d] Yields of purified compounds (recrystallization). [e] $[\alpha]^{23}_D$ −50.0 (*c* 0.2, H_2O/TFA 90:10).

To gain mechanistic insight into these transformations, we carried out a multinuclear NMR monitoring of the reaction of α-azidomethylphosphonate **1** with cyclohexyldichloroborane (**7**).[12] The NMR spectra taken immediately after mixing at −30 °C indicated the clean formation of the expected complex **24** (Scheme 3).[13] Heating of the sample

Scheme 3



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(3) For some selected and recent syntheses of racemic and optically active α-aminomethylphosphonic acids and esters: (a) Uziel, J.; Genêt, J.-P. *Russ. J. Org. Chem.* **1997**, *33*, 11521. (b) Yokomatsu, T.; Minowa, T.; Yoshida, Y.; Shibuya, S. *Heterocycles* **1997**, *44*, 111. (c) Boduszek, B. *Phosphorus Sulfur Silicon Relat. Elem.* **1997**, *122*, 27. (d) Seki, M.; Kondo, K.; Iwasaki, T. *J. Chem. Soc., Perkin Trans. 1* **1996**, 3. (e) Aller, E.; Buck, R. T.; Drysdale, M. J.; Ferris, L.; Haigh, D.; Moody, C. J.; Pearson, N. D.; Sanghera, J. B. *J. Chem. Soc., Perkin Trans. 1* **1996**, 2879. (f) Mikolajczyk, M.; Lyzwa, P.; Drabowicz, J.; Wieczorek, M. W.; Blaszczyk, *J. Chem. Soc., Chem. Commun.* **1996**, 1503. (g) Couture, A.; Deniau, E.; Woisel, P.; Grandclaudon, P. *Tetrahedron Lett.* **1995**, *36*, 2483. (h) Takahashi, H.; Yoshioka, M.; Imai, N.; Onimura, K.; Kobayashi, S. *Synthesis* **1994**, 763. (i) Groth, U.; Lehmann, L.; Richter, L.; Schöllkopf, U. *Liebigs Ann. Chem.* **1993**, 427. For some recent syntheses of optically active *β*-aminoethylphosphonic, see ref 2a,b.

(4) Alternative method of deprotection in the presence of trialkylsilyl halides: McKenna, C. E.; Higa, M. T.; Cheung, N. H.; McKenna, M. C. *Tetrahedron Lett.* **1977**, *18*, 155.

(5) Preparation of *N*-alkyl-α-aminomethylphosphonic acids by Mannich-type reactions of primary amines with formaldehyde and phosphorous acids: (a) Moedritzer, K.; Irani, R. R. *J. Org. Chem.* **1966**, *31*, 603. (b) Courtois, G.; Miginiac, L. *Synth. Commun.* **1991**, *21*, 201. Condensation reactions of corresponding primary amines with α-chloromethylphosphonic acids: (c) Schwarzenbach, G.; Ackermann, A.; Ruckstuhl, P. *Helv. Chim. Acta* **1949**, *32*, 1175. (d) Fredericks, P. M.; Summers, L. A. *Z. Naturforsch. C* **1981**, *36*, 242. Reaction of *N*-alkyl-*N*-hydroxymethylformamides with phosphorus trichloride: (e) Tyka, R.; Hägele, G. *Synthesis* **1984**, 218.

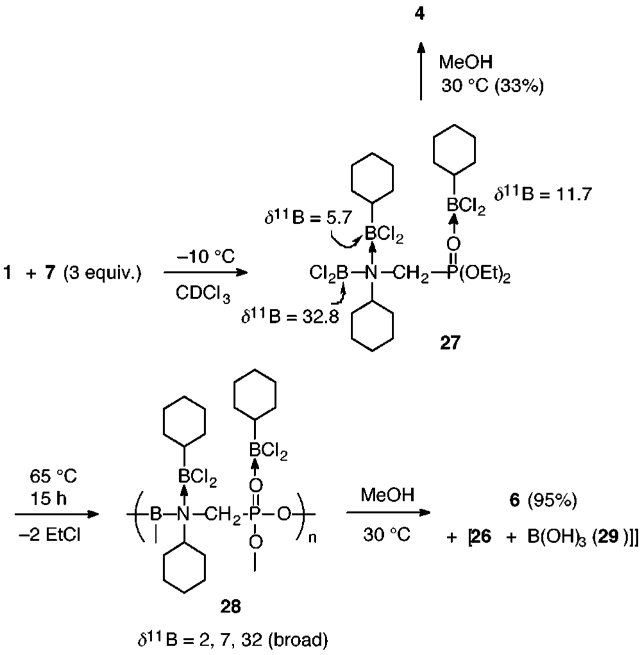
(6) Preparation of *N*-alkyl-*β*-aminoethylphosphonic acids by phosphorylation of *β*-bromoalkylamines with chlorophosphates: Brigot, D.; Collignon, N.; Savignac, P. *Tetrahdron* **1979**, *35*, 1345.

(7) (a) Suzuki, A.; Sono, S.; Itoh, M.; Brown, H. C.; Midland, M. M. *J. Am. Chem. Soc.* **1971**, *93*, 4329. (b) Brown, H. C.; Midland, M. M.; Levy, A. B.; Suzuki, A.; Sono, S.; Itoh, M. *Tetrahedron* **1987**, *43*, 4079.

containing**24** for 15 h at 65 °C was accompanied by evolution of ethyl chloride (detected in ^{1}H and ^{13}C NMR) and led to dramatic changes in NMR spectra: broad resonances in ^{1}H, ^{13}C, ^{11}B, and ^{31}P NMR spectra indicated the presence of a polymeric material **25** with tetracoordinated boron ($\delta^{11}B = -4$), tetracoordinated phosphorus ($\delta^{31}P = 0$), and untouched azido group (unchanged ^{14}N spectrum). Methanolysis of the reaction mixture gave α-azidomethylphosphonic acid (**3**) and cyclohexylboronic acid (**26**). Thus, reaction of **1** with 1 equiv of **7** does not result in the reductive alkylation of the azido group but instead gives a polymer **25**, similar to those recently synthesized either by reaction of trialkylboranes with phosphonic acids[14] or by treatment of silyl esters of phosphonic acids with alkyldichloroboranes.[15]

Addition of 3 equiv of **7** to 1 equiv of **1** at −10 °C resulted in a vigorous evolution of nitrogen. The ^{1}H and ^{13}C NMR of the reaction mixture displayed the signals of a cyclohexyl CHN group [$\delta^1H = 3.70$ (tt, $^3J_{aa} = 11.5$ Hz, $^3J_{ae} = 3.1$ Hz), $\delta^{13}C = 57.67$ (d, $^3J_{CP} = 12.0$ Hz)]. Integral intensities in the ^{1}H NMR spectrum showed two ethoxy groups and three cyclohexyl rings for one CH_2P group. No signals of azido group were found in the ^{14}N spectrum. In the ^{11}B spectrum, three signals of equal intensity at 5.7, 11.7, and 32.8 ppm were observed. The chemical shift in phosphorus NMR ($\delta = 26.17$) is near to that in complex **24** ($\delta = 24.53$). We conclude that the observed NMR spectra correspond to complex **27** (Scheme 4). Methanolysis of this sample gave diethyl *N*-cyclohexyl-α-aminomethylphosphonate (**4**) with small admixtures of semiester **5** and phosphonic acid **6**. Thus, in the reaction of **1** with 3 equiv of **7**, the reductive alkylation takes place prior to ethoxy groups cleavage, and selective preparation of **4** is possible if the reaction is carried out at −10 °C.

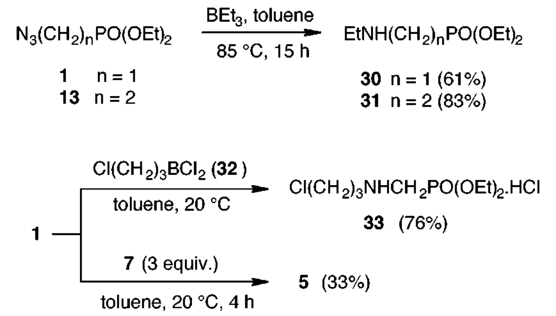
Scheme 4



Broad resonances in the ^{1}H, ^{13}C, ^{11}B, and ^{31}P NMR spectra of the sample obtained after 15 h heating at 65 °C indicated the formation of a polymer. The phosphorus spectrum displayed two broad maxima at $\delta = 22$ ($LW_{1/2} = 1200$ Hz) and 38 ($LW_{1/2} = 600$ Hz), both corresponding to pentavalent phosphorus. These two maxima in the phosphorus spectrum may be due to the presence of species with and without coordinated cyclohexyldichloroborane or, for example, cyclic and noncyclic oligomers. In the boron spectrum, an extremely broad resonance centered at approximately 32 ppm was detected together with two sharp signals of unequal intensity at 2 and 7 ppm. The methanolysis of this sample gave *N*-cyclohexyl-α-aminomethylphosphonic acid (**6**) in excellent yield (95%) together with cyclohexylboronic acid (**26**) and boric acid (**29**). These data allow us to conclude that the hydrolysis of ethoxyphosphonate groups observed together with the reductive alkylation of azidoalkylphosphonates proceeds via polymer **28**, which in contrast to **24** contains pentavalent phosphorus and trivalent boron.

Having in mind the established mechanism of methanolysis, by appropriate choice of reagents and conditions one can selectively prepare any of the compounds of the type **2**−**6**.[16] Additionally, *N*-ethylaminoalkylphosphonates **30** and **31** were prepared by treating azidophosphonates **1** and **13**, respectively, with triethylborane (Scheme 5). The reaction of 3-chloropropyldichloroborane (**32**) and α-azidomethylphosphonate (**1**) at 20 °C for 4 h gave **33**, whereas treating cyclohexyldichloroborane (**7**) (3 equiv) at 20 °C for 15 h produced selectively monoester **5**.

Scheme 5



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[8] **1** was obtained by treatment of diethyl α-iodomethylphosphonate (Lancaster) with sodium azide in DMSO: Berté-Verrando, S.; Nief, F.; Patois, C.; Savignac, P. *Phosphorus, Sulfur, Silicon* **1995**, *103*, 91.

[9] Alkyldichloroboranes were prepared in situ from corresponding alkene, BCl_3, and Et_3SiH: Soundararajan, R.; Matteson, D. S. *Organometallics* **1995**, *14*, 4157.

[10] Preparation of *N*-methyl-α-amino acid derivatives from α-azido acids, amides, and esters with Me_2BBr: Dorow, R. L.; Gingrich, D. E. *J. Org. Chem.* **1995**, *60*, 4986.

[11] **13** was prepared by reaction of diethyl β-bromoethylphosphonate (Lancaster) with sodium azide: Ohashi, K.; Kosai, S.; Arizuka, M.; Watanabe, T.; Yamagiva, Y.; Kamikawa, T. *Tetrahedron* **1989**, *45*, 2557.

[12] For the NMR experiments, **7** was synthesized by hydroboration of cyclohexene with $HBCl_2$ in the presence of BCl_3: Brown, H. C.; Ravindran, N.; Kulkarni, S. U. *J. Org. Chem.* **1980**, *45*, 384.

In conclusion, a general approach to *N*-alkyl/aryl-α- and β-aminoalkylphosphonic acids has been presented, based on the treatment of boranes with azidophosphonates. The cleavage of diethylphosphonates can be conducted for the first time with dichloroboranes. We are in the progress of further delineating the scope of this reaction in addition to preparing other N-substituted aminoalkylphosphonic acids from azidoalkylphosphonic acid derivatives.

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(13) Spectral data for diethyl azidomethylphosphonate-cyclohexyldichloroborane complex (**24**): ^{1}H NMR (300 MHz, $CDCl_3$, 297 K) δ 0.64 (tt, 1H, CHB, $^{3}J_{aa} = 11.7$ Hz, $^{3}J_{ae} = 2.7$ Hz), 1.06 (m, 2H of cyclohexyl), 1.19 (m, 4H of cyclohexyl), 1.45 (t, 6H, $2CH_3$, $^{3}J = 7.1$ Hz), 1.70 (br m, 4H of cyclohexyl), 1.81 (m, 2H of cyclohexyl), 4.17 (d, 2H, CH_2P, $^{2}J = 11.4$ Hz), 4.55 (m, 4H, $2CH_2O$); ^{13}C NMR (75 MHz, $CDCl_3$, 300 K) δ 16.19 (d, $2CH_3$, $^{3}J_{CP} = 5.4$ Hz), 27.20, 27.79, 28.72 ($3CH_2$ of cyclohexyl), 35.5 (br, CHB), 45.07 (d, CH_3P, $^{1}J_{CP} = 155.8$ Hz), 66.5 (br, $2CH_2O$); ^{31}P NMR (121 MHz, $CDCl_3$, 297 K) δ 24.53; ^{11}B NMR (96 MHz, $CDCl_3$, 297 K) δ 11.7; ^{14}N NMR (22 MHz, $CDCl_3$, 297 K) δ −332 (br), −164.8, −135.3.

(14) Walawalkar, M. G.; Murugavel, R.; Roesky, H. W.; Schmidt, H.-G. *Organometallics* **1997**, *16*, 516.

(15) Diemert, K.; Englert, U.; Kuchen, W.; Sandt, F. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 241.

(16) **Representative Experimental Procedure.** Preparation of *N*-cyclohexyl-α-aminomethylphosphonic acid hydrochloride (**6**). In a round-bottom flask under argon, a mixture of triethylsilane (2.49 mL, 15.6 mmol) and cyclohexene (1.28 g, 15.6 mmol) previously cooled at −78 °C was added dropwise to neat trichloroborane (1.82 g, 15.6 mmol) at −78 °C. The resulting reaction mixture was allowed to warm over a period of 2 h to room temperature. In a second flask equipped with a condenser and purged under argon was introduced diethyl α-azidomethylphosphonate (**3**) (155 mg, 0.80 mmol, 1 M in toluene). Dichloroborane **7** (2.4 mmol, 1 M in toluene) was added dropwise, and the resulting mixture was stirred for 15 h at 85 °C. The solution was slowly allowed to warm to room temperature, and dry methanol (325 μL, 8 mmol) was added. Addition of dry ether (5 mL) gave a white precipitate that was filtered and dried. *N*-Cyclohexyl-α-aminomethylphosphonic acid hydrochloride (**6**) was recrystallized with $MeCN-MeOH-H_2O$ (95%): mp 235 °C dec; ^{1}H NMR (D_2O, 300 MHz) δ (ppm) 1.19−1.38 (m, 5H), 1.58−1.67 (m, 1H), 1.76−1.86 (m, 2H), 2.02−2.18 (m, 2H), 3.11−3.23 (m, 1H), 3.14 (d, 2H, $^{1}J_{HP} = 13.1$ Hz); ^{13}C NMR (D_2O, 50 MHz) δ (ppm) 24.4, 24.8, 28.9, 40.9 ($^{1}J_{PC} = 139.0$ Hz), 59.2 ($^{3}J_{PC} = 6.9$ Hz); ^{31}P NMR (D_2O, 121 MHz) δ (ppm) 10.4; HRMS calcd for $C_7H_{17}NO_3P$ 194.0946, found 194.094; SM (LSIMS) *m*/*z* 194.1 $[M + H^+]$.