Highly Selective Amination of 1-Primary, 3-Secondary 1,3-Alkanediols. A New Approach to 3-Aminoalkyl 4-Nitrobenzoates

Tadeusz Gajda

Institute of Organic Chemistry, Technical University (Politechnika), Żwirki 36, PL-90-924 Łódź, Poland

1-Primary, 3-secondary 1,3-alkanediols can be selectively aminated at C-1 via OH/NH_2 exchange by reaction with diethyl *N*-Boc-phosphoramidate in ether using triphenylphosphine/diethyl diazenedicarboxylate as condensing agent, and treatment of the resultant diethyl *N*-Boc-*N*-(3-hydroxyalkyl)phosphoramidates with 4-nitrobenzoyl chloride/pyridine, followed by dephosphorylation with hydrogen chloride in ethyl acetate. The reaction sequence affords the hydrochlorides of 3-aminoalkyl 4-nitrobenzoates in good yields.

Substituted 3-aminoalkanols possessing primary or secondary amino groups have been of considerable interest for some time, because they frequently exhibit interesting pharmacological properties.[1] The 3-aminoalkanol unit with a primary amino group is present in several classes of natural products, e.g., in aminosugars, aminopolyols,[2,3] and α-amino-γ-hydroxycarboxylic acids.[4]

The synthesis of such 3-aminoalkanols has been accomplished by a variety of methods, e.g., reduction of 3-hydroxyalkanamides,[5] 3-hydroxyaldehyde *O*-alkyloximes,[6] β-oxygenated nitriles,[7,8] 3-azidoalkanols,[9] and β-aminocarbonyl compounds,[10] reductive cleavage of the N–O bond of isoxazolidines,[11] cycloaddition of nitrile oxides to alkenes followed by stereoselective reduction of the resultant isoxazolines,[2,3,12] conversion of 1,3-dicarbonyl compounds into their monoalkyloximes followed by reduction,[13] or regiospecific opening of substituted epoxides by α-metallated isocyanides and hydrolysis of the 3-hydroxyalkyl isocyanides[14] thus formed.

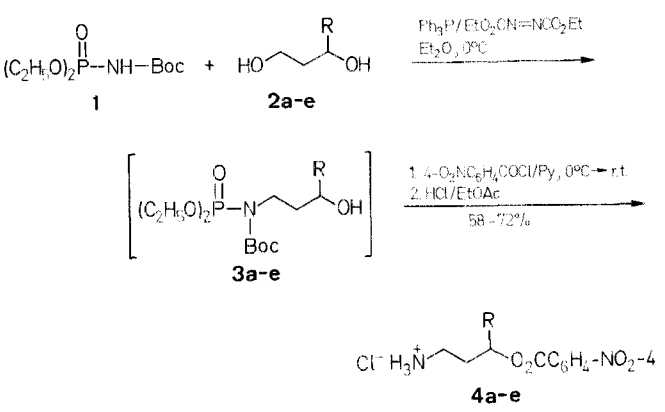
All of these methods may have some limitations as regards the structure of the desired aminoalcohols and there is still a need to develop new methods for the preparation of this class of compounds.

I report here the use of diethyl *N*-(*tert*-butoxycarbonyl)phosphoramidate (**1**) for the direct transformation of 1,3-alkanediols into 3-aminoalkanol derivatives utilizing the triphenylphosphine/diethyl azodicarboxylate (diethyldiazenedicarboxylate) system.[15]

The use of reagent **1** provides a versatile alternative to the Gabriel-type synthesis of primary amines from alkyl bromides[16] and to the direct transformation of primary and secondary alcohols to the corresponding amines according to Mitsunobu (reaction of the alcohol with diethyl *N*-(*tert*-butoxycarbonyl) phosphoramidate in the presence of triphenylphosphine/diethyl azodicarboxylate and cleavage of the resultant *N*-alkylation product with dry hydrogen chloride in benzene[17]). Some aminosugars[15] and derivatives of phytospingosine[18] have been obtained by phthaloylamination of partially *O*-protected carbohydrates or diols.

The triphenylphosphine/diethyl azodicarboxylate system can in general activate the alcohol by formation of a dialkoxytriphenylphosphorane[19–22] which is in equilibrium with the corresponding alkoxytriphenylphosphonium salt,[20–22] and which can alkylate suitable acidic components under mild and neutral conditions.

Reagent **1** is readily *N*-alkylated to form phosphoramidates **3a–e** when diethyl azodicarboxylate is added to the mixture of **1**, the corresponding 1,3-diol **2a–e**, and triphenylphosphine in diethyl ether. The slightly exothermic reaction proceeds smoothly at 0°C; its progress can be followed by the precipitation of diethyl hydrazine-*N*,*N*′-dicarboxylate and triphenylphosphine oxide and also by the color change of the reaction mixture from



2,3,4	a	b	c	d	e
R	H	CH_3	C_2H_5	n-C_3H_7	$CH_2C_6H_5$

Table. 3-Aminoalkyl 4-Nitrobenzoate Hydrochlorides **4** Prepared

Product	Yield[a] (%)	m.p. (°C)[b] (solvent)	Molecular Formula[c]	IR (KBr)[d] ν(cm^{-1})	^{1}H-NMR (D_2O/TMS_{ext})[e] δ, J(Hz)
4a	72	180–182 ($EtOH/Et_2O$, 1:1)	$C_{10}H_{13}ClN_2O_4$ (260.7)	2980, 1720, 1600, 1520, 1340, 1270, 1115	2.5 (br. dt, 2H, J = 5.9, 7.6, CH_2); 3.53 (t, 2H, J = 7.6, CH_2N); 4.8 (t, 2H, J = 5.9, CH_2O); 5.01 (br. s, NH_3); 8.43–8.69 (AA'BB' of p-C_6H_4, 4H)
4b	68	199–201 ($EtOH/Et_2O$, 1:3)	$C_{11}H_{15}ClN_2O_4$ (274.7)	2960, 1720, 1605, 1525, 1350, 1280, 1105	1.74 (d, 3H, J = 6.3, CH_3); 2.46 (m, 2H, CH_2); 3.5 (br. t, 2H, J = 7.8, CH_2N); 5.01 (br. s, NH_3); 5.57 (sext, 1H, J = 6.3, CH); 8.40–8.60 (AA'BB' of p-C_6H_4, 4H)
4c	59	169–170 ($EtOH/Et_2O$, 1:4)	$C_{12}H_{17}ClN_2O_4$ (288.7)	2940, 1715, 1605, 1525, 1345, 1280, 1110	1.26 (t, 3H, J = 7.3, CH_3); 2.11 (br. quin, 2H, J = 7.3, CH_2); 2.47 (m, 2H, CH_2); 3.45 (t, 2H, J = 7.8, CH_2N); 5.01 (br. s, NH_3); 5.47 (quin, 1H, J = 6.3, CH); 8.44–8.68 (AA'BB' of p-C_6H_4, 4H)
4d	58	170–171 ($EtOH/Et_2O$, 1:1)	$C_{13}H_{19}ClN_2O_4$ (302.8)	2940, 1715, 1600, 1520, 1475, 1340, 1275, 1095	1.03 (t, 3H, J = 6.5, CH_3); 1.34–1.69 (m, 2H, CH_2); 1.89 (m, 2H, CH_2); 2.44 (m, 2H, CH_2); 3.42 (br. t, 2H, J = 8, CH_2N); 5.01 (br. s, NH_3); 5.44 (m, 1H, CH); 8.10–8.31 (AA'BB' of p-C_6H_4, 4H)
4e	62	174–175 ($EtOH/Et_2O$, 3:1)	$C_{17}H_{19}ClN_2O_4$ (350.8)	3000, 1720, 1605, 1525, 1355, 1270, 1100, 720	2.49 (m, 2H, CH_2); 3.26–3.57 (m, 4H, CH_2N + CH_2Ph); 5.01 (br. s, NH_3); 5.71 (quin, 1H, J = 6.4, CH); 7.51 (br. s, $5H_{arom}$); 8.21–8.46 (AA'BB' of p-C_6H_4, 4H)

[a] Yield of isolated product, based on **1**.
[b] Uncorrected, measured in capillaries.
[c] Satisfactory microanalyses obtained: C ±0.24, H ±0.15, N ±0.28.
[d] Recorded on a Specord 71IR (C. Zeiss) spectrophotometer.
[e] Recorded at 90 MHz using a Bruker HX-Series 72 (FT) spectrometer.

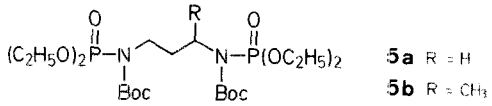
orange to pale yellow. It is not necessary to isolate the intermediates **3a–e** before cleavage to the amine hydrochlorides **4a–e**. The crude phosphoramidates **3a–e** can be directly converted into the easily isolable hydrochlorides of the 3-aminoalkyl 4-nitrobenzoates **4a–e** by reaction with 4-nitrobenzoyl chloride in pyridine followed by removal of the phosphoryl group with hydrogen chloride[16] in ethyl acetate.

The overall yields of amine hydrochlorides **4a–e** from 1,3-diols **2a–e** are in the range of 58–72%.

In the case of the primary/secondary 1,3-diols **2b–e**, OH/NH_2 exchange by means of **1** occurred regioselectively at the primary hydroxy group, giving the phosphoramidates **3b–e** exclusively. The regioisomeric purity of products **3b–e** was evident from the ^{31}P-NMR spectra.

All phosphoramidates **3b–e** gave a single sharp ^{31}P-NMR peak (between $\delta_{31_P} = +2.2$ and $\delta_{31_P} = +2.7$) in the expected region (there were also two minor peaks at $\delta_{31_P} \approx +27$ and $\delta_{31_P} \approx -2.0$, corresponding to the signals of triphenylphosphine oxide and unreacted **1**, respectively).

The reaction of 1,3-propanediol **(2a)** with reagent **1** under the same conditions is less selective, the monoalkylated, major product **3a** ($\delta_{31_P} = +2.25$) being contaminated with 20% of the dialkylated compound **5a** ($\delta_{31_P} = +1.71$).



5a R = H
5b R = CH_3

Nevertheless, the amine hydrochloride **4a** can be easily isolated in pure form and in high yield (72%).

Triphenylphosphine seems to be the phosphine component of choice for our method. Use of tributylphosphine under the same conditions led to a dramatic loss of selectivity. For example, amination of 1,3-butanediol **(2b)** in the presence of tributylphosphine afforded a 60:40 mixture of **3b** and **5b** (^{31}P-NMR).

The highly selective mono-amination of 3-alkyl-1,3-propanediols can be interpreted in terms of the transient formation of cyclic 1,3-alkanediyldioxytriphenylphosphoranes, existing in equilibrium with the corresponding primary and secondary alkoxytriphenylphosphonium salts.[21,22] Hence, further reaction with **1**, which seems to proceed by an S_N2 process, occurs exclusively at the primary alkoxy group of the alleged primary alkoxytriphenylphosphonium salt intermediate.[15] The presence of two equivalent primary hydroxy groups in 1,3-propanediol and the formation of the cyclic 1,3-propanediyldioxytriphenylphosphorane, together with some acyclic or macrocyclic phosphorane oligomers,[22] is probably responsible for the decreasing selectivity in the amination of 1,3-propanediol. These activated phosphoranes, by way of the respective 3-hydroxypropyloxytriphenylphosphonium salts, can possibly compete in the reaction with **1**, giving mixtures of the mono- and dialkylated products **3a** and **5a**.

Because of the use of an acid-labile protective group (phosphoramidate) for the introduction of the N-atom our method might complement the method based on the phthaloylamination reaction.[18] Its principal advantage is that the target 3-aminoalkanol derivatives are easily obtained in high purity and under neutral and mild conditions.

^{1}H-NMR and ^{31}P-NMR spectra were recorded on a Bruker HX-Series 72 (FT) spectrometer at 90 and 36.43 MHz respectively. Negative ^{31}P chemical shifts (δ_{31_P}) are upfield from external phosphoric acid (85%). Diethyl *N*-(*tert*-butoxycarbonyl)phosphoramidate **(1)** was prepared according to the previously described procedure[16] from diethyl phosphorcyanatidate and *tert*-butyl alcohol. Diethyl azodicarboxylate (diethyl diazenedicarboxylate) was obtained by the established procedure.[23]

1,3-Alkanediols 2:

1,3-Propanediol and *1,3-butanediol* are commercially available (Fluka) and were distilled before use. The other 1,3-diols were prepared accord-

ing to Lit.[24] by reduction of the respective methyl 3-oxoalkanoates with sodium borohydride in MeOH/THF.

1,3-Pentanediol (**2c**); yield: 48% (67% in small-scale preparation); b.p. 78–81°C/1 Torr; n_D^{20}: 1.4444 (Lit.[25], yield: 33%; b.p. 84°C/2 Torr; n_D^{20}: 1.4448).

1,3-Hexanediol (**2d**); yield: 26% (60% in small-scale preparation); b.p. 70–73°C/0.2 Torr; n_D^{20}: 1.4448 (Lit.[26], yield: 30%; b.p. 85–90°C/0.3 Torr; n_D^{20}: 1.4455).

4-Phenyl-1,3-butanediol (**2e**); yield: 71%; b.p. 128–131°C/0.5 Torr; n_D^{20}: 1.5371.

$C_{10}H_{14}O_2$ (166.2) calc. C 72.26 H 8.81
found 72.15 8.65

^{1}H-NMR ($CDCl_3$/TMS): δ = 1.55 (m, 2H, CH_2); 2.65 (d, 2H, J = 6.7 Hz, CH_2Ph); 3.62 (t, 2H, J = 6.2 Hz, CH_2O); 3.71 (br.s, 2H, 2 × OH); 3.88 (m, 1H, CH); 7.15 (s, 5H_{arom}).

3-Aminoalkyl 4-Nitrobenzoate Hydrochlorides 4a–e; General Procedure:

A solution of diethyl azodicarboxylate (1.92 g, 0.011 mol) in Et_2O (5 mL) is added dropwise with stirring and external cooling (ice-water bath) to a mixture of diethyl *N*-(*tert*-butoxycarbonyl)phosphoramidate (**1**; 2.53 g, 0.01 mol), triphenylphosphine (2.88 g, 0.011 mol), the 1,3-alkanediol **2** (0.011 mol), and Et_2O (30 mL) at 0°C over a period of 30 min. The mixture becomes pale yellow and a white precipitate is formed. After the addition is completed, the mixture is stirred at 0°C for 1 h, and then is left overnight at room temperature. Hexane (80 mL) is added to the mixture and the precipitate is filtered off. The filtrate is evaporated in vacuo to give the crude phosphoramidate **3** as a pale yellow oil. This material is dissolved in dry pyridine (25 mL), the solution is cooled to 0°C, 4-nitrobenzoyl chloride (2.32 g, 0.0125 mol) is added in one portion, and the mixture is stirred for 20 h at room temperature. Pyridine is then removed under reduced pressure. To the semisolid residue, benzene (50 mL) is added and the solution is carefully washed with 5% HCl/H_2O (2 × 20 mL) and H_2O (3 × 20 mL). The organic layer is separated, dried (Na_2SO_4), and evaporated under reduced pressure. The oily residue is treated with EtOAc (50 mL), and saturated with gaseous HCl. The mixture is left overnight at room temperature. Excess HCl and the solvent are removed in vacuo and anhydrous Et_2O (80 mL) is added to the residue. The crystalline precipitate **4** is isolated by suction, washed with Et_2O (2 × 20 mL), and recrystallized from EtOH/Et_2O.

The author acknowledges financial support of this work by a grant, MR-I.12.1.3.1/2, from the Polish Academy of Sciences.

Received: 6 April 1987; revised: 23 June 1987

(1) Korner, J.K., Otis, L., Skinner, W.A. *J. Med. Chem.* **1967**, *10*, 38.
(2) Jäger, V., Schohe, R. *Tetrahedron* **1984**, *40*, 2199.
(3) Jäger, V., Buss, V., Grund, H., Schwab, W., Müller, I. *Bull. Soc. Chim. Belg.* **1983**, *92*, 1039; *C.A.* **1984**, *100*, 139561.
(4) Roberts, D.C., Vellaccio, F., in: *The Peptides*, Gross, E., Meienhofer, J. (eds.), Academic Press, New York, 1983, Vol. 5, Part B, Chapter 6, pp. 341–449.
(5) Pankova, M., Tichy, M. *Collect. Czech. Chem. Commun.* **1974**, *39*, 1447.
(6) Sato, H., Kusumi, T., Imaye, K., Kakisawa, H. *Bull. Chem. Soc. Jpn.* **1976**, *49*, 2815.
(7) Bassus, J., Pacheco, H., Chaveire, M., Cier, A. *Eur. J. Med. Chem.-Chim. Ther.* **1974**, *9*, 416; *C.A.* **1975**, *82*, 112017.
(8) Boiko, I.P., Khasirdzhev, A.B., Zhuk, O.I., Malina, Y.F., Samitov, Y.Y., Unkovski, B.V. *Zh. Org. Khim.* **1977**, *13*, 327.
(9) Alewood, P.F., Benn, M., Reinfried, R. *Can. J. Chem.* **1974**, *52*, 4083.
(10) Tramontini, M. *Synthesis* **1982**, 605.
(11) DeShong, P., Dicken, C.M., Leginus, J.M., Whittle, R.R. *J. Am. Chem. Soc.* **1984**, *106*, 5598.
(12) Jäger, V., Buss, V. *Liebigs Ann. Chem.* **1980**, 101, 122.
(13) Secor, H.V., Sanders, E.B. *J. Org. Chem.* **1978**, *43*, 2539.
(14) Schöllkopf, U., Jentsch, R., Madawinata, K., Harms, R. *Liebigs Ann. Chem.* **1976**, 2105.
(15) Mitsunobu, O. *Synthesis* **1981**, 1; and references cited therein.
(16) Zwierzak, A., Pilichowska, S. *Synthesis* **1982**, 922.
(17) Ślusarska, E., Zwierzak, A. *Liebigs Ann. Chem.* **1986**, 402.
(18) Mulzer, J., Brand, C. *Tetrahedron* **1986**, *42*, 5961.
(19) Grochowski, E., Hilton, B.D., Kuper, R.J., Michejda, C.J. *J. Am. Chem. Soc.* **1982**, *104*, 6876.
(20) von Itzstein, M., Jenkins, I.D. *Aust. J. Chem.* **1983**, *36*, 557.
(21) Robinson, P.L., Barry, C.N., Woody Bass, S., Jarvis, S.E., Evans, S.A. *J. Org. Chem.* **1983**, *48*, 5398.
(22) von Itzstein, M., Jenkins, I.D. *J. Chem. Soc., Perkin Trans. 1* **1986**, 437.
(23) Rabjohn, N. *Org. Synth. Coll. Vol. III*, **1955**, 375.
(24) Soai, K., Oyamada, H. *Synthesis* **1984**, 605.
(25) Mellin, M., Davidson, M., Lumbroso, D., Giuliani, P., Coussemant, F. *Bull. Soc. Chim. Fr.* **1964**, 2974.
(26) von Rudolf, E. *Can. J. Chem.* **1958**, *36*, 486.