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OPTICALLY ACTIVE α-AMINOPHOSPHONIC ACIDS FROM UREIDOPHOSPHONATES

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The preparation of both levorotatory and dextrorotatory α-aminobenzylphosphonic acid by the hydrolysis of substituted ureidophosphonates is described. This method represents an alternative to phosphite addition to unsaturated C-N compounds.

Several approaches to the preparation of optically active α-aminophosphonic acids have been attempted. Resolution of the amino esters followed by hydrolysis has been successful for α-aminobenzylphosphonic acid[1,2] as well as asymmetric synthesis from optically active Schiff bases[3,4]. The absolute configuration of optically active α-aminobenzylphosphonic acid has likewise been determined[4]. By far, the less troublesome process of asymmetric synthesis is preferable for preparation of optically active α-aminophosphonic acids as opposed to resolution. However, the only asymmetric synthetic method reported to date for an α-aminophosphonic acid is that employed for the preparation of α-aminobenzylphosphonic acid mentioned above.

In our continuing program concerned with the synthesis of α-aminophosphonic acids, and in particular, optically active α-aminophosphonic acids, we are constantly searching for more synthetic approaches to these compounds. We recently reported[5] the synthesis of α-aminophosphonic acids from ureidophosphonates and now wish to report, as an extension of this method, the first reported synthesis of an optically active α-aminophosphonic acid, α-aminobenzylphosphonic acid, from ureidophosphonates.

The method which we report here is based on the acid catalyzed reaction of substituted ureas with trivalent phosphorus esters and aldehydes to give ureidophosphonates as originally described by Birum[6] (Scheme I). Subsequent hydrolysis and neutralization affords the free α-aminophosphonic acid (3). Thus, when optically active ureas derived from R and S α-methylbenzylamine (1) are employed the reaction as in Scheme I with benzaldehyde affords optically active α-aminobenzylphosphonic acid. The requisite ureas are prepared by the cyanate method[7]

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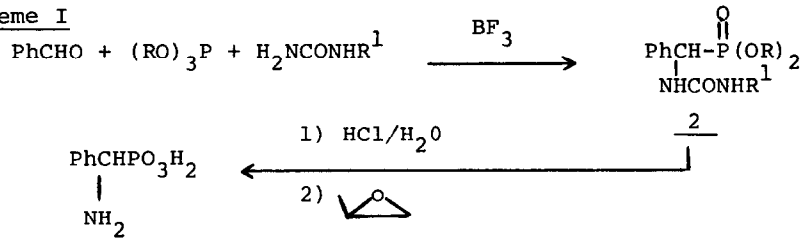
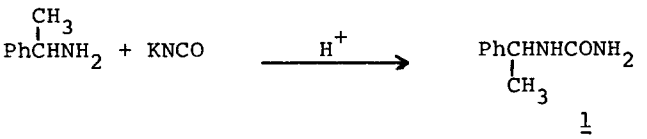
(Scheme II) from the parent amine and potassium cyanate.

Scheme I



a. R^1 = (R) - PhCH(CH$_3$)—; R = Et- b. R^1 = (S) - PhCH(CH$_3$)—; R = Et-

Scheme II



The method outlined here thus provides an additional example of the preparation of optically active α-aminobenzylphosphonic acid other than by the phosphite addition method[3]. Work on the extension of this method to the preparation of other optically active α-aminophosphonic acids is currently in progress. Although the optical activity of the product is less than that observed with the phosphite addition method (see Experimental), it is interesting to note that in the method we report here, the relationship between the sign of observed rotation of product aminophosphonic acid and starting amine is opposite that of the phosphite addition method[3,4]. These results are summarized in Table 1.

Table 1

Method	Amine[a]	Observed Rotation
Phosphite Addition	R	-
	S	+
Ureidophosphonate Hydrolysis	R	+
	S	-

a Absolute configuration of α-methylbenzylamine used in synthesis

Experimental

All melting points are uncorrected. Infrared spectra were recorded on a Perkin-Elmer 257 grating infrared spectrophotometer. NMR spectra were obtained at 60 MHz using a Perkin-Elmer R-24-A spectrometer using as solvent either D_2O (containing one drop of 40% NaOD/D_2O) or $CDCl_3$. Peaks are reported relative to sodium 2,2-dimethyl-2-silapentane-5-sulfonate (D_2O) or TMS ($CDCl_3$). Mass spectra were obtained at 70 eV on a Dupont 321 gas chromatograph-mass spectrometer equipped with a Dupont 320 data system. Polarimetric analyses were performed on a Perkin-Elmer 141 automatic digital recording polarimeter. Elemental analyses were performed by Galbraith Laboratories, Inc., Knoxville, TN.

The benzaldehyde was obtained from Aldrich Chemical Company and was distilled prior to use. The triethyl phosphite, boron trifluoride etherate and α-methylbenzylamines were also purchased from Aldrich.

Preparation of α-Methylbenzyl Ureas (1a and 1b): To an ice-cooled mixture of 50 g(0.41 mol) of either R-(+)-($[\alpha]_D^{20}$ + 39°, neat) or S-(-)-($[\alpha]_D^{20}$ - 39°, neat) α-methylbenzylamine, 36.5 g (0.45 mol) of potassium cyanate and 500 ml of water was added slowly 100 ml of 5 N hydrochloric acid with constant stirring. The resulting solution was allowed to come to room temperature after which it was heated to almost boiling for 3 hrs. The resulting solution was cooled to room temperature and then in a refrigerator for several hours. Filtration of the mass followed by drying in a vacuum oven afforded 57 g (81%) of the urea. Recrystallization from water gave analytical samples: mp 124-125° [lit.[8] mp 123.5-124°]; ir (Nujol) 700,750 (Ar), 1560 - 1600 (NH), 1650 (C=O), 3300-3430 (NH_2); nmr ($CDCl_3$) 7.35 (s, 5 H, C_6H_5), 5.5 (broad, 1 H, NH-), 4.75 (m, 1 H, CH_3CH-), 1.5 (d, 3 H, J = 7 Hz, CH_3CH-); Mass spectra gave molecular ions at m/e 164.

R-$[\alpha]_D^{25}$ + 47.5°(c=2, 95% EtOH) [lit.[9] $[\alpha]_D^{25}$ + 48.8° (c = 2.2%, 95% EtOH)]

Anal: Calcd for $C_9H_{12}N_2O$: C, 65.84; H, 7.36; N, 17.06. Found: C, 66.00; H, 7.39; N, 16.99.

S - $[\alpha]_D^{25}$ - 41.9° (c = 2, 95% EtOH)

Anal: Calcd for $C_9H_{12}N_2O$: C, 65.84; H, 7.36; N, 17.06. Found: C, 65.96; H, 7.51; N, 16.92.

(+)- α-Aminobenzylphosphonic Acid (3a): To a mixture of 8.2 g (0.05 mol) of the R-urea, 5.3 g (0.05 mol) benzaldehyde, 8.3 g (0.05 mol) triethyl phosphite and 110 ml toluene was added dropwise, with constant stirring, a solution of 2.5 ml boron trifluoride etherate in 20 ml toluene over 15 minutes. After stirring an additional 15 minutes at room temperature, the solution was heated to reflux where it was kept for 4 hrs. The cooled solution was filtered, concentrated in vacuo followed by stripping (0.1 mm) on a steam bath. To the straw-yellow, viscous syrup was added 250 ml of concentrated hydrochloric acid and the mixture stirred at reflux for 72 hrs. The resulting solution was filtered and the filtrate washed with two 25-ml portions of methylene chloride. The acidic aqueous layer was concentrated in vacuo to a thick suspension. To this was added approximately 100 ml of ethanol followed by portionwise addition of propylene oxide until a final pH of 6 was reached. After cooling in the refrigerator for 1 hr., the suspension was filtered and the collected solid dried in a

vacuum oven affording 4.4 g (47% based on benzaldehyde) of crude phosphonic acid. Recrystallization from water-ethanol gave an analytical sample: mp 287-288° [lit.[3,10] mp 280-282°]; ir (Nujol) 1220 (P=O) cm^{-1}; nmr (D_2O/NaOD) δ 4.0 (d, 1 H, J = 16 Hz, ArCHP) and 7.55 ppm (m, 5 H, C_6H_5-); mass spectra (70 eV) of the N-trifluoroacetyl (N-TFA) diethyl ester derivative[11] gave a molecular ion at M/e 339; $[\alpha]_D^{25}$ + 3.3° (c = 2, 1 N NaOH) [lit[3,4] $[\alpha]_D^{25}$ + 18.1°, $[\alpha]_D^{25}$ - 18° (c = 2, 1 N NaOH]

(-) - α-Aminobenzylphosphonic Acid (3b): The procedure outlined above for 3a was followed with the exception that the S-urea was employed. The product had identical mp, ir, nmr, and ms (N-TFA diethyl ester) as did 3a. $[\alpha]_D^{25}$ - 3.50 (c = 2, 1 N NaOH [lit[3,4] $[\alpha]_D^{25}$ - 18.1°, $[\alpha]_D^{25}$ - 18°, (c = 2, 1 N NaOH)]

BIBLIOGRAPHY

1. M.K. Rho and Y.J. Kim, Taehan Hwahak Hoechi, 19, 434 (1975).
2. S.V. Roghozin, V.A. Davankov and Yu.P. Belov, Izv. Akad. Nauk SSSR, Ser. Khim., 1973, 955; Chem. Abstr., 79, 42610k.
3. W.F. Gilmore and H.A. McBride, J. Amer. Chem. Soc., 94, 4361 (1972).
4. T. Glowiak, W.S. Dobrowolska, J. Kowalik, P. Mastalerz, M. Soroka and J. Zon, Tetrahedron Lett., 1977, 3965.
5. J.W. Huber, III, and M. Middlebrooks, Synthesis, 1977, 883.
6. G. Birum, J. Org. Chem., 39, 209 (1974).
7. K. Kurzer, Org. Synth. Coll. Vol IV, 49 (1963).
8. A.P. Terentev, R.A. Gracheva and V.T. Bezruchko, Zh. Org. Khim., 5, 1063 (1969); Chem. Abstr. 71, 69992h (1969).
9. T.L. Cairns, J. Amer. Chem. Soc., 63, 871 (1941).
10. a. J. Lukszo, and R. Tyka, Synthesis, 1977, 239.
    b. R. Tyka, Tetrahedron Lett., 1970, 677.
11. J. W. Huber, III, J. Chromatogr., 152, 220 (1978).

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