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Phosphonylmethylaminocyclopentane-1-carboxylic Acid

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ABSTRACT: *Phosphonylmethylaminocyclopentane-1-carboxylic acid was synthesized using Kabachnik–Fields reaction conditions in high yield and was characterized by NMR (^1H, ^{31}P, and ^{13}C) and FAB spectroscopy.* © 2003 Wiley Periodicals, Inc. Heteroatom Chem 14:229–230, 2003; Published online in Wiley InterScience (www.interscience.wiley.com). DOI 10.1002/hc.10124

INTRODUCTION

Aminophosphonic acids constitute an important class of biologically active compounds, and their synthesis has been a focus of considerable attention in synthetic organic chemistry as well as in medicinal chemistry. They are considered to be structural analogues of amino acids and transition state mimics of peptide hydrolysis. Numerous applications have been found for aminophosphonic acids. Herbicidal activity of *N*-phosphonomethyl glycine is reported by Baird [1]. It is effective in inhibiting test-tube growth of *Plasmodium falciparum*, the parasite that causes malaria [2]. It has the same effect on related types of single-celled parasites such as *Toxoplasma* and *Cryptosporidium* that case opportunistic infections in AIDS patients [3]. It has been found that the *N*-phosphonomethyl glycine derivatives are especially effective in suppressing the growth of the cancer, tumor, virus, or bacteria [4]. The use of these *N*-phosphonomethyl glycines in combination with other chemotherapeutic agents that are effective in destroying the tumor is a novel method of treatment. It is known that aminophosphonic acids penetrate the membranes of cancer cells 4–5 times more easily than that of normal cells [5]. Aminocyclopentane-1-carboxylic acid, cycloleucin, is a well-known antitumor agent [6]. Examination of the literature shows that Maier et al. have described the synthesis of phosphonylmethylaminocyclopropane-1-carboxylic acid [7] and phosphonylmethylaminocyclohexane-1-carboxylic acid [8].

In this article, we describe the synthesis of phosphonylmethylaminocyclopentane-1-carboxylic acid **1** using Kabachnik–Fields reaction conditions.

RESULTS AND DISCUSSION

First, aminocyclopentane-1-carboxylic acid was treated with paraformaldehyde in the presence of triethylamine in methanol. When the reaction mixture became homogeneous, diethyl hydrogen phosphonate was added. The reaction proceeded to afford the diethyl ester of **1**. Its alkali hydrolysis furnished **1** in a good yield (86%) (Scheme 1).

The structure of **1** was established by ^1H, ^{31}P, and ^{13}C NMR spectroscopy (see Experimental). The $^{13}C\{H\}$ NMR signal at $\delta = 3.72$ ppm can be assigned to the tertiary carbon atom, and the one at $\delta =$ 175.70 ppm to the carbon atom of the carboxyl group. Both signals disapper in the DEPT spectrum. The FAB spectrum shows a signal at $MH^+ = 192$.

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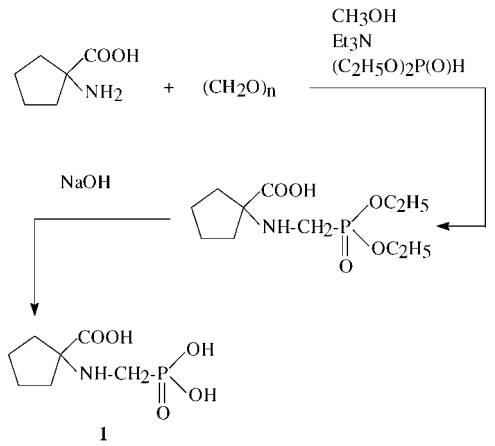

SCHEME 1 Synthesis of phosphonylmethylaminocyclopentane-1-carboxylic acid.

EXPERIMENTAL

Diethyl hydrogen phosphonate and triethylamine were distilled prior to use.

Aminocyclopentane-1-carboxylic acid was synthesized by cyclopentanespiro-5-hydantoin alkaline hydrolysis [9]. The structure was proved by ^{1}H and ^{13}C{H} NMR spectroscopy. ^{1}H NMR (D_2O), δ in ppm: 1.63–2.10 (m, 8H, CH_2). ^{13}C NMR (D_2O), δ in ppm: 25.15 C3 and C4; 34.6 C2 and C5; 66.9 C1; 178.3 COOH. ^{1}H, ^{13}C, and ^{31}P NMR spectra were recorded on a Bruker DRX 500 spectrometer in D_2O.

Synthesis of **1**

Paraformaldehyde (0.6 g, 0.02 mol), methanol (15 ml), and triethylamine (0.2 ml) were put into a three-necked flask equipped with a condenser, magnetic stirrer, and thermometer. The reaction mixture was heated to reflux temperature and held there for 45 min, after which it became a clear solution. To this solution was added aminocyclopentane-1-carboxylic acid (1.59 g, 0.0123 mol) and triethylamine (1.23 g, 0.0123 mol). This suspension was then heated at 65–70°C and after 30 min it became a clear solution. To this solution was added diethyl hydrogen phosphonate (1.12 g, 0.081 mol) over a period of approximately 10 min. The reaction mixture was heated at 65–70°C and held there for 2.5 h, after which it was cooled to room temperature, and while stirring, sodium hydroxide (3.08 g, 40% water solution) was added. The reaction mixture was heated at 105–110°C for 5 h. Subsequently, it was treated with Dowex 50WX8-200 in order to exchange the sodium cations by hydrogen ions. The water was removed under vacuum to give 1.81 g (95%) of **1**, m.p. = 224–225°C.

^{1}H NMR (D_2O), δ in ppm: 1.73–2.25 (m, 8H, CH_2); 3.16 (d, 2H, ^{2}J(P,H) = 14.6 Hz), P—CH_2.

^{13}C{H} NMR (D_2O), δ in ppm: 25.75 C3 and C4; 34.85 C2 and C5; 41.68 (d, ^{1}J(P,C) = 136.2 Hz) P—CH_2; 73.72 C1; 175.70 C=O.

^{31}P{H} NMR (D2O), δ in ppm: 10.51.^{31}P NMR (D_2O), δ in ppm:10.49 (t, ^{2}J(P,H) = 13.6 Hz).

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