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A New Non-Chloride Method of Synthesis of Antibacterial Antibiotic Fosfomycin Based on the Principles of Green Chemistry

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Abstract—A new non-chloride method for synthesis of antibacterial antibiotic fosfomycin, which is based on principles of green chemistry, has been developed.

Keywords: green chemistry, non-chloride method, antibiotics, fosfomycin
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INTRODUCTION

Green chemistry is a new area of chemistry and chemical engineering, which emerged in the 1990s and is focused on redesigning chemical processes and products in the manner that enhances the environmental performance. Along these lines, new schemes of chemical reactions and processes, intended to drastically reduce the environmental impact of large chemical plants, have been developed in many laboratories around the world [1, 2]. Accordingly, the underlying strategy of green chemistry is that of careful selection of raw materials and process schemes in which the use of substances hazardous to human health and environment is avoided [3, 4]. Consistent application of the green chemistry principles leads to lower production costs due to elimination of the steps involving destruction and processing of harmful byproducts, spent solvents, and other wastes which are formed in negligible amounts. Reduction in the number of synthesis steps leads to energy saving, which also contributes to better results of environmental and economic assessment of the production [5–7].

Green chemistry principles are also successfully used today in the chemical synthesis of drugs, above all of antibiotics [8–12]. One known drug produced synthetically is a low-toxic organophosphorus broad spectrum antibacterial antibiotic fosfomycin [(–)-(1*R*, 2*S*)-(1,2-epoxypropyl) phosphonic acid] [13–17] which is used for treatment of many infectious diseases caused by gram-positive and gram-negative bacteria [18–20]. In recent years, fosfomycin has been extensively applied for treating infections in combinations with other antibacterial antibiotics (cephalosporins, aminoglycosides, tetracyclines, and fluoroquinolones), whereby the therapeutic effect of these agents is increased, and their toxicity, reduced [21–23]. Today, fosfomycin certainly remains popular among clinicians [24–26], being, in particular, the drug of choice for treatment of urinary tract infections, especially acute cystitis [27–31].

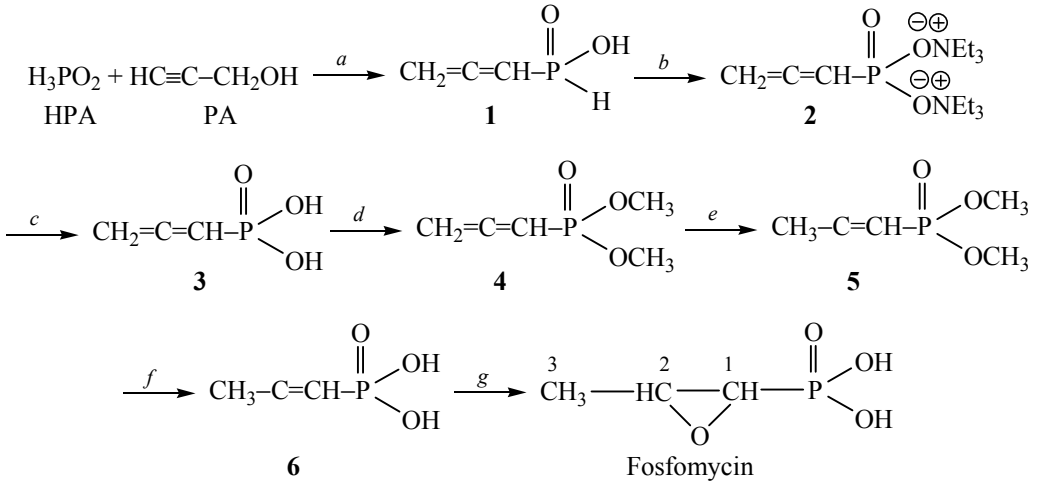
There exist numerous synthetic routes to fosfomycin, mostly based on the use of highly toxic, harsh chemicals such as phosphorus trichloride PCl_3 [32–37] and its derivatives $(BuO)_2PCl$ [38] and $ClCH_2P(O)Cl_2$ [39, 40]. Other halogenated reactants, e.g., 2-chloropropionaldehyde [41], thionyl chloride ($SOCl_2$) [42–44], and epibromohydrin [45], also find widespread use for fosfomycin synthesis.

The aim of this study was to develop a new method for the synthesis of fosfomycin basing on the chlorine-free chemistry approaches, with the use of nontoxic chemicals in compliance with green chemistry principles.

EXPERIMENTAL

We used chemicals available from Sigma-Aldrich (US) or Fluka (Switzerland) without further purifica-

Scheme 1. Synthesis of antibacterial antibiotic fosfomycin.



a: C_6H_6, 80°C; *b*: CCl_4, Et_3N, H_2O, 20°C; *c*: Dowex H^+, H_2O, 20°C; *d*: CH_2N_2, diethyl ether–methanol, 0°C; *e*: H_2, Pd/C, MeOH, 20°C; *f*; HCl (10% aqueous solution), 60°C; and *g*: CF_3CO_3H, 0°C.

tion. Organic solvents were purified before use by the techniques from [46].

The ^1H and ^{13}C NMR spectra were obtained on a Bruker Avance III (FRG) instrument (operating frequency 600 MHz) from 10–15% solutions in D_2O or MeOH-d_4, with TMS as internal standard. For recording the ^{31}P NMR spectra we used a Bruker AC-200 (FRG) instrument operating at 200 MHz frequency; chemical shifts $\delta(^{31}P)$ were referenced to 85% H_3PO_4 external standard. The MALDI–TOF mass spectra were measured on a MALDI Micromass (US) spectrometer with α-cyano-4-hydroxycinnamic acid matrix. The IR spectra were recorded on a Bruker vector 22 (FRG) instrument from samples pressed into KBr pellets. To monitor the progress of the reaction and the identity of the compounds obtained we used the TLC technique on Silica Gel 60 F_{254} (0.25 mm, Merck, FRG) plates in different solvent systems: chloroform-methanol 9 : 1; chloroform–methanol 5 : 1; and chloroform-methanol-ammonium hydroxide (25% aqueous solution) 10 : 3 : 1. Substances were detected in the chromatograms using UV light or iodine vapor, with Silica Gel 60 sorbent (63–200 mm, Merck, FRG). The melting point (decomposition temperature) was determined on an Electrothermal IA9300 (UK) instrument.

RESULTS AND DISCUSSION

The fosfomycin synthesis by the method developed by us was started with propargyl alcohol (PA) which reacted with hypophosphorous acid (HPA) (Scheme 1) to yield 1,2-propadienylphosphonous acid **1** as a result of hydrophosphoryl acetylene-allene rearrangement detected by us earlier [47–49]. As phosphorylating compound we used hypophosphorous acid which is a mild hydrophosphorylating agent [50]. The reaction proceeded under vigorous stirring in benzene at 80°C under reflux using a Dean–Stark trap. The second step consisted in oxidation of the phosphorus-hydrogen bond of **1** under the Atherton–Todd reaction conditions [51, 52]. The resulting triethylammonium salt of 1,2-propadienylphosphonic acid **2** was dissolved in distilled water and passed through a column packed with Dowex H^+ cation exchange resin to obtain free acid **3** which was further reacted with diazomethane to synthesize 1,2-propadienylphosphonic acid methyl ester **4** following the procedure from [53, 54]. The reaction of hydrogenation of **4** with the use of Pd/C catalyst in methanol at room temperature [55] led to 1,2-propenephosphonic acid methyl ester **5**. Acid hydrolysis of **5** with 10% hydrochloric acid under the conditions described in [50, 56] yielded 1,2-propene-phosphonic acid **6**. The epoxidation reaction of **6** using trifluoroperacetic acid [57] gave antibiotic fosfomycin (Scheme 1).

[(–)-(1*R*, 2*S*)-(1,2-Epoxypropyl)phosphonic acid] (fosfomycin). ^1H NMR spectrum (D_2O), δ, ppm: 1.47 d (3H, $J_{1,2}$ = 5.0 Hz, H^3), 2.83 d.d (1H, $J_{2,3}$ = 5.5 Hz, $J_{H^1–P}$ = 19.0 Hz, H^1), 3.27 m (1H, H^2). ^{13}C NMR spectrum (D_2O), δ, ppm: 16.35 (C^3), 57.25 (C^2), 57.67 d (C^1, $J_{C^1–P}$ = 175 Hz). ^{31}P NMR spectrum (D_2O), δ, ppm: 11.17. Mass spectrum (MALDI TOF): calculated

for $C_3H_7O_4NaP$ $[M + Na]^+$, *m/z* 161.05, found 161.07. The ^1H, ^{13}C, and ^{31}P NMR spectral parameters of fosfomycin obtained by the method developed by us were fully consistent with the published data [58–62]. The melting point of benzylammonium salt of fosfomycin was 172–174°C (recrystallization from methanol–water mixture, 1 : 1) against 170–174°C reported in the literature [14].

CONCLUSIONS

Thus, the non-chloride method of synthesis of antibacterial antibiotic fosfomycin, developed by us, employs readily available technologically and environmentally acceptable nontoxic chemical raw materials, in compliance with the principles of green chemistry.

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