Microwave Modern Synthesis of Diphenyl (2-hydroxyphenyl) (octylamino) methylphosphonate

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Summary

The synthesis of α-aminophosphonic acids and their derivatives have an increasing interest because they are mimetics of the natural α-amino acids. Compound diphenyl (2-hydroxyphenyl)(octylamino)methylphosphonate, is obtained by reacting salicylaldehyde with n-octylamine to form the Schiff base, after that the Schiff base is reacted with diphenylphosphite. The compound is characterized by melting point, IR, and NMR. Keywords: mimetics of α-amino acids, α-aminophosphonates synthesis, Schiff base

Introduction

The α-aminophosphonic acids are considered to be ones of the most important natural amino acids’ mimetics, the peptides and proteins key blocks building into the life chemistry.

Because of their reduced toxicity and ability to substitute natural amino acids in the competition for the enzyme’s active sites or other receptors the α-aminophosphonates (α-
aminophosphonic acids and their derivatives) are used as enzymes inhibitors [1], natural amino acids’ mimetics [2], as well as medicines (bisphosphonates with P–C–P bonds for the treatment of osteoporosis), [3]. They are also used for metal complexing (platinum (II) complexes present anticancer activity [3], metals separation and concentration agents [4], antioxidants [5], pesticides [6], herbicides or plant growth regulators [7], ions matrix recognition [8], contrast agents in the nuclear magnetic resonance imagistic control of ill living human and animal bodies [9], pipe scale inhibition [10], radioprotecting agents [11], etc. The α-aminophosphonic acids and as well as their derivatives, the aminophosphonates, from which are obtained by acid hydrolysis, present some different properties related to the corresponding natural amino acids as:

- structural differentiation (phosphonic group has a tetrahedral structure versus the flat structure of the carboxyl group);
- higher acidity (phosphonic group is more acidic than the carboxylic group);
- different volumes (the phosphorous atom has a bigger radius than the carbon atom).

**Materials and Methods**

The proton spectrum was obtained using a 400 MHz VARIAN GEMINI spectrometer. Chemical shifts were obtained in ppm and the coupling constants in Hz. Infrared spectrum was recorded using KBr pellets on a Carl Zeiss-Jena SPECORD M-80 IR spectrometer. Melting point was determined on a digital apparatus of type Electrothermal IA9100. Salicylaldehyde and n-octylamine were purchased from Fluka and diphenylphosphite from Aldrich. TLC plates type Kieselgel F254 with fluorescence indicator were obtained from Merck. The microwave energy in the reaction was obtained using a domestic microwave oven of 850 W power and 2450 MHz working frequency.

**Reaction working procedure:** In a 50 mL Erlenmeyer are stirred 10 mmol salicylaldehyde, 12 mmol n-octylamine and 10 mmol diphenylphosphate. The vessel was hermetically closed using a silicon septum. The vessel is placed into the owen and then heated 5 times for 30 seconds, at 600 W. The vessel’s content is cooled slowly at the room temperature, then eluted with ethanol, filtered and repeatedly washed with ethylic alcohol and chlorophorm until a white powder is obtained. The diphenyl (2-hydroxiphenyl)(octylamino) methylphosphonate (5) yields was 77%.

**Diphenyl (2-hydroxiphenyl)(octylamino) methylphosphonate (5):** fine white powder; **m.p.** = 286–288°C; **1H-NMR (400 MHz, DMSO, δ, ppm):** 7.1 – 7.3 (m, 4H, Ar); 6.8 – 6.9 (m, 10H, Ar), 4.2 (d, 2H, P–CH–NH–(CH2)7–CH3), 2.6 (bp, 2H, CH–NH–CH2–(CH2)6–CH3), 1.5, 1.2, 0.8 (3s, 15H, NH–CH2–(CH2)6–CH3); **IR (KBr, cm⁻¹):** ν:
3428i w (OH) intense wide band; 1610i (aromatic nucleus); 1460 (nucleus’ vibrations); 1214i (P=O); 1085i, 1056i, 958i (P–O–C aromatic); 892i (monosubstituted benzene); 766i, 744i (ortho disubstituted benzene) cm⁻¹.

**RESULTS AND DISCUSSION**

The aminophosphonates can be obtained by using the Strecker synthesis, when aldehydes react with ammonia and dialkylphosphites [12], by reaction of N-substituted thiourea with an aldehyde and triphenylphosphites [13, 14], by addition of dialkylphosphites to preformed Schiff bases [15], the reaction of cyclohexanone with an amine and diethylphosphite to obtain α-aminocycloalkylphosphonates [16, 17], as well as by the reaction of an aldehyde with diethylphosphite and ammonium bicarbonate (when ammonia is generated *in situ*) using the microwave energy [18-22].

Aminophosphonates microwave assisted synthesis has many advantages, over classical synthesis: the reactions’ times are much shorter (2-6 minutes, instead of 6-12 hours or quite days); concurrent and parallel reactions are minimized, so the reactions products are more pure and the purification steps are reduced; very high reaction yields.

**Figure 1. The reaction steps synthesis of diphenyl (2-hydroxiphenyl)(octylamino) methylphosphonate**
The classic synthesis of diphenyl (2-hydroxiphenyl) (octylamino) methylphosphonate realized in two step reaction was previously communicated [25]. When is used the energy of microwaves, the reaction type was „one pot reaction”, what means that all three reactants are introduced in the same time, finally being obtained the aminophosphonates without the isolation of the intermediates. Schiff base in situ generated was not isolated, but its formation and consumption was monitored by thin layer chromatography (TLC). By the same procedure was appreciated the compound purity before to use other physic-chemical characterizations. The compound obtained as a racemic, was isolated, recristalized and then characterized by melting point, IR and ¹H-RMN spectroscopy. The investigation by IR spectroscopy evidenciated the characteristic band vibrations ν for P=O and P–O–C, which are in concordance with compounds from the same class [23, 24]. The aminophosphonate structure by ¹H-RMN investigation was evidenciated by chemical shifts and protons’ number after integration.

Conclusion

Diphenyl (2-hydroxiphenyl)(octylamino) methylphosphonate obtained by this modern way, using the microwave energy is easy to be used, ecologic (because is not using toxic solvents and the reaction yield is more then good. The reaction time is drastically reduced to 3-5 minute instead of 6-12 hours in the classic way [25]. This new synthesized compound, not cited in the literature, was characterized by melting point, infrared spectroscopy and proton nuclear magnetic resonance.

Reference