Synthesis of radiolabeled aromatic bisphosphonates and their potential application in bone metastasis pain palliation.

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Summary

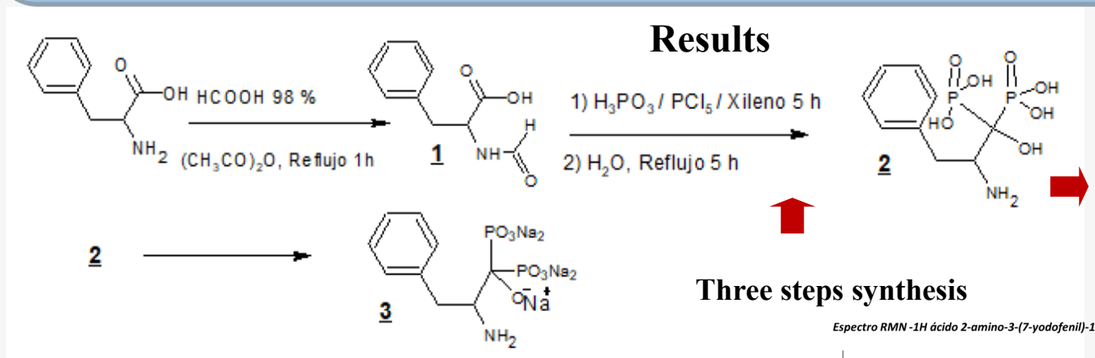
- The use of radiopharmaceuticals for bone metastatic pain palliation have shown significant advantages.
- Bone metastases is the most common complication of oncological diseases. They are usually incurable, produce severe pain, decreasing the expectancy and quality of life of patients.
- Bisphosphonates are the main compounds employed for that purpose; nevertheless, their synthesis is a elatively complex process.
- A three-steps way of synthesis was stablished for the obtainment of such compounds: 1) protection of amino group of the starting amino acid, 2) phosphonation and subsequent hydrolysis of the protected amino group and 3) obtainment of sodium salt.
- Bisphosphonic acids, non-previously reported in consulted literature, were synthetized. They were characterized by infrared spectroscopy and NMR

Method

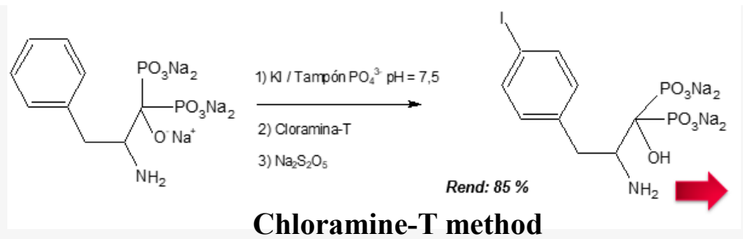
The relative distances to the solvent front (Rf) were calculated and reported for the different mobile phases both on paper and silica gel. The melting temperatures were determined in an Electrothermal equipment, 9100 model.

The infrared spectra were recorded on an ATI Mattson Genesis Series Fourier transform spectrometer (FTIR) in the range of 400 to 4000 cm-1. The ^{1}H-NMR spectra were recorded on a Bruker model AC model, 13 MHz. The samples were dissolved in deuterated dimethylsulfoxide (DMSO-d6). The labeling yield was calculated with TLC in 1 x 12 cm strips and as solvent the chloroform: methanol (10: 2) system. The speed of counts in the strip fractions, in the ^{131}I labels, was determined in a ScalerTimer ST-7 single-channel radiometer.

Results

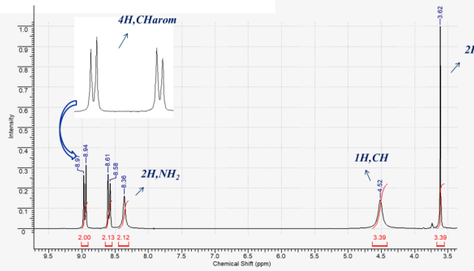


Three steps synthesis



Chloramine-T method

Espectro RMN -1H ácido 2-amino-3-(7-yodofenil)-1-hidroxipropil-1,1-bifosfónico



Equipo de la marca Bruker modelo AC 250F (Alemania) a 250,13 y 62,8 MHz, respectivamente.

Conclusions

The aminolysis reaction was effective in the process of protecting the amino group of L-phenylalanine.

It was corroborated that from a mixture of phosphorous acid and phosphorus pentachloride, it is possible to perform the phosphonation of 3-phenyl-2-formylamidopropionic acid with satisfactory yields.

It was possible to obtain the sodium salt of 2-amino-3-phenyl-1-hydroxypropyl-1,1-bisphosphonic acid by neutralization reaction with sodium hydroxide in suitable yields and purity.

By chloramine-T method it was possible to obtain 2-amino-3- (7-iodophenyl) -1-hydroxypropyl-1,1-bisphosphonic acid with satisfactory yield and purity.

References

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Método sencillo para la síntesis de bisfosfonatos geminales. Revista CENIC. Ciencias Químicas, vol. 47, pp. 34-42. Centro Nacional de Investigaciones Científicas. La Habana, Cuba http://www.redalyc.org/pdf/1816/181648522005.pdf