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SYNTHESIS OF PENICILLIN G FROM STYROFOAM (POLYSTYRENE)

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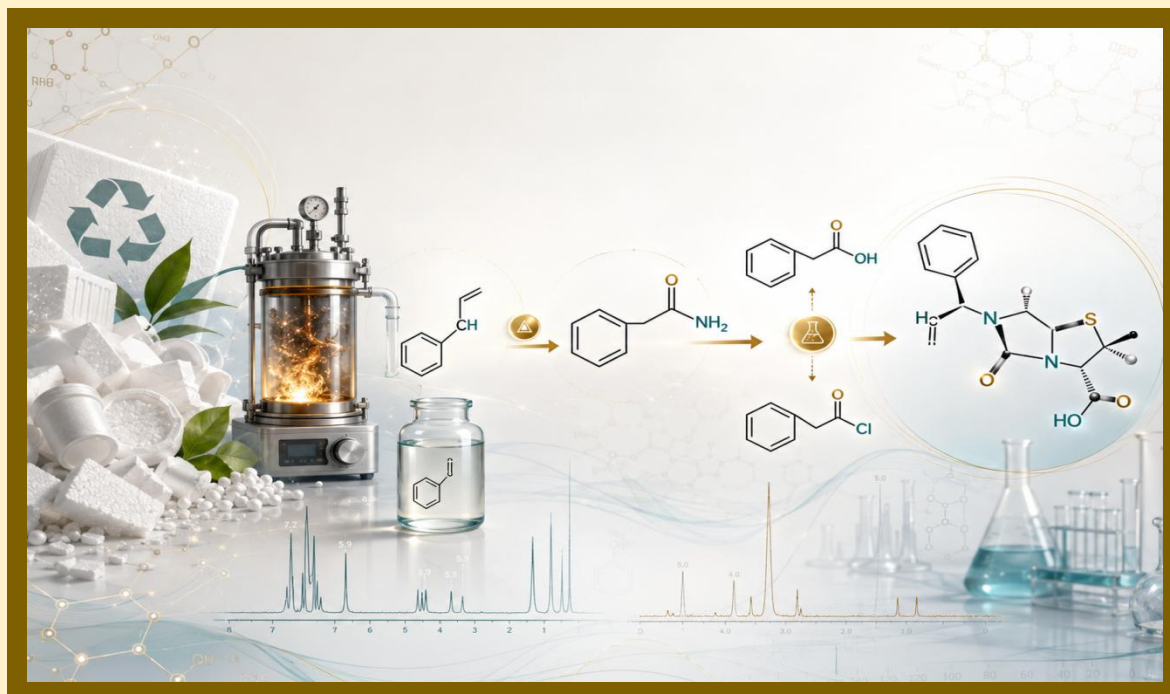
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Abstract

In the world, each person produces on average about 1 kg of waste per day. In Brazil, this production varies from 450 to 1,200 grams per inhabitant/day, generating more than 228 thousand tons/day (Moraes et al., 2018). Of the more than 100,000 tons of polystyrene polymer resin produced per year (in Brazil alone), only 34 thousand tons are recycled per year in our country (Albuquerque & Guedes, 2021). What to do with the other 66 thousand tons of non-recycled polystyrene (Isopor®)? By applying "pyrolysis to Styrofoam", which consists of converting very low-density solid waste into liquid (styrene), making it more compact (dense), moldable, and easy to store and transport. By subjecting styrene to the "Willgerodt reaction", which due to its common characteristic of converting carbonyl compounds into an amide with the same number of carbon atoms, it is possible to synthesize 2-phenylacetamide, which will later serve as a structural block for the synthesis of class "C" penicillin.

One way to alleviate the problem (recycling) is to apply pyrolysis, which consists of converting very low-density solid waste into liquid, making it more compact (dense), moldable and easy to store and transport. Pyrolysis consists of depolymerizing and cracking materials through high temperatures in the total absence of oxygen, where a molecular rearrangement occurs generating a pyrolytic oil with high energy potential (Scheirs, et al., 2006), figure-1.

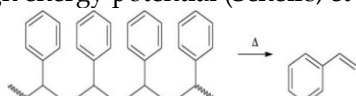


Figure - 01: Polystyrene being converted into styrene by pyrolysis, source: MOLDOVEANU, 2010.

The Willgerodt reaction was first described by Conrad Willgerodt in 1887. The reaction involves the oxidation/rearrangement of a ketone to form a terminal amide or the ammonium salt of the corresponding carboxylic acid (Willgerodt, 1887). Today, Conrad Willgerodt's name is associated with a group of closely related reactions that have as a common feature the conversion of a carbonyl compound to an amide with the same number of carbon atoms (Figure - 02, Willgerodt, 1887).

Therefore, this approach has the potential to generate a variety of pharmacologically relevant thioamides in a single step. It is also worth noting that the WK reaction allows a type of "umpolung" in which the carbonyl is reduced while the terminal methyl group is oxidized, starting with acetophenone, for example. The element sulfur and an amine, such as morpholine, are used in the similar Willgerodt-Kindler reaction, figure -2.

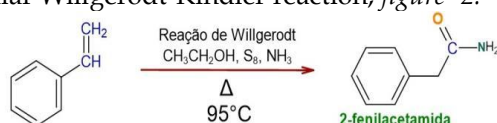


Figure - 02: Willgerodt reaction. For the synthesis of 2-phenylacetamide; in addition to styrene (starting reagent), elemental sulfur, ammonia solution and methyl alcohol (solvent) are added to an autoclave, source: Author's own.

Starting from 2-phenylacetamide obtained from styrene via the Willgerodt route, the next structural block to be synthesized to obtain Penicillin G is phenylacetic acid, which is easily obtained by refluxing it with a strong acid that will hydrolyze the acetamide into its corresponding acid.

In the next step, the phenylacetic acid will react under anhydrous conditions with thionyl chloride to form Phenylacetyl chloride, figure-04.

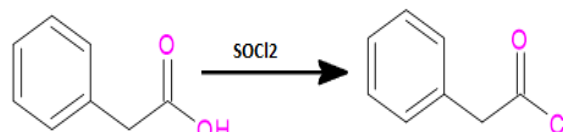


Figure-04, Source: Author's own

Finally, the phenylacetyl chloride that was synthesized from the polystyrene polymer will serve as a structural block for the formation of class "C" Penicillin. The proposal is to carry out the synthesis in anhydrous conditions using chloroform as the solvent and pyridine as the neutralizing agent for the HCl formed in the synthesis reaction, figure-05.

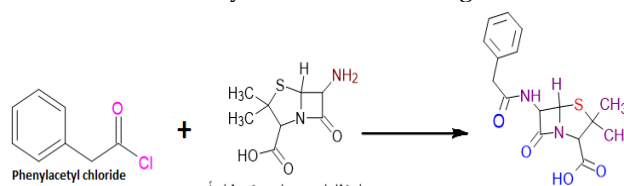


Figure - 05, Source: Author's own

The Willgerodt synthesis (already achieved in this project) is the most challenging when compared to other established routes such as polystyrene pyrolysis, acid hydrolysis of 2-phenylacetamide for conversion into its corresponding acid, chlorination of phenylacetic acid (phenylacetyl chloride) and the synthesis of penicillin G. Therefore, below are the data on the characterization of 2-phenylacetamide synthesized

in the laboratory of the State University of Mato Grosso do Sul – Brazil by the Willgerodt route.

Characterization of 2-phenylacetamide by ^{13}C -NMR DEPT-135 and discussion

The recrystallized 2-phenylacetamide was analyzed by ^{13}C DEPT-135 NMR to confirm the proposed synthesis. Through the spectrum, it was possible to verify that the purification and recrystallization were successfully obtained, since carbon-hydrogen signals with chemical shift were obtained that correspond only to the structure of 2-phenylacetamide; these shifts were observed between 128 to 130 (referring to the aromatic ring) and close to 43, referring to carbon-hydrogen, referenced in Figure 05 and Table 01, as being the letter "a". These values obtained from the NMR spectra were verified according to the book with the following title: Nuclear Magnetic Resonance (NASCIMENTO, 2016).



Figure-05: ^{13}C NMR spectrum – DEPT 135 for 2-phenylacetamide.

Table 01: Characterization of 2-phenylacetamide by ^{13}C DEPT-135 NMR

δ Químico (ppm)	Organic Function
128 a 130	Aromatic ring
43	Folding carbon

Characterization of 2-phenylacetamide by ^1H and ^{13}C NMR and discussion

The recrystallized 2-phenylacetamide was analyzed by ^1H -NMR to confirm the proposed synthesis. Through the ^1H -NMR spectrum, it was possible to verify that the purification and recrystallization were successful, since hydrogen signals with chemical shifts were obtained that correspond only to the structure of 2-phenylacetamide. Observing the NMR spectrum, the shifts were identified at 3.7 ppm for the carbon hydrogens ($-\text{CH}_2$), at 5.5 to 5.9 ppm for the amine hydrogens ($-\text{NH}_2$), and at 7.52 to 7.07 for the

aromatic ring hydrogens. The spectrum is shown in Figure-06 and Table 02 below. These values obtained from the NMR spectra were verified according to the book with the following title: "Nuclear Magnetic Resonance" (NASCIMENTO, 2016).

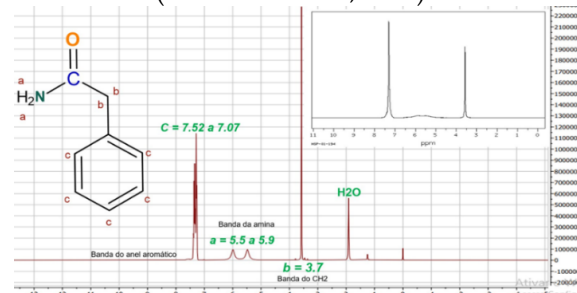


Figure - 06: ^1H NMR spectrum obtained for 2-phenylacetamide.

Table 02: Characterization of 2-phenylacetamide by ^1H -NMR.

δ Químico (ppm)	Organic Function
C7, 4	Aromatic ring
5,5 a 6,0	Amine
3,7	Folding Carbon
1,9	Water Molecule

Characterization of 2-phenylacetamide by ^{13}C -NMR and discussion

The recrystallized 2-phenylacetamide was analyzed by ^{13}C NMR to confirm the proposed synthesis. Through the spectrum obtained, it was possible to verify that the purification and recrystallization were successfully obtained, since chemical shift bands of carbon 13 were obtained with a shift corresponding only to the structure of 2-phenylacetamide. The signals that were observed close to 173 ppm correspond to the carbonyl carbon band; from 127 to 135 ppm corresponding to the aromatic ring band; and the carbon band between the aromatic ring and the acetamide at 43 ppm (Figure -07 and Table 03). These values obtained from the NMR spectra were verified according to the book with the following title: "Nuclear Magnetic Resonance" (NASCIMENTO, 2016).

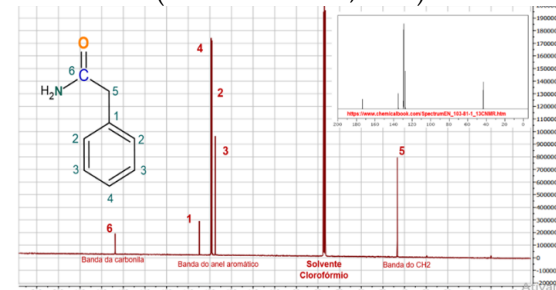


Figure-07: ^{13}C -NMR spectrum obtained for 2-phenylacetamide.

Tabela 03: Caracterização da 2-fenilacetamida por RMN-¹³H.

δ Químico (ppm)	Organic Function
174	carbonyl band
127 a 135	Aromatic ring
78	Solvent
43	Folding carbon

As the data extracted in the characterizations proved to be positive for the synthesis of 2-phenylacetamide through the Willgerodt reaction, and it is known that it composes and contemplates the purpose of the structural block of the synthetic molecule of Penicillin G, it is now sufficient to continue with the reactions already established to achieve the objective in the synthesis of the proposed antibiotic.

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