



Comparison of two synthesis methods of a pharmaceutical excipient used as conservative

Derouicha Matmour^{1,2}, Nadia Cherchali¹, Imane Belayachi¹, Toumi Houari²

¹Therapeutic Chemistry Laboratory, Pharmacy Department, 22000 Sidi Bel-Abbes, Algeria

²Research Laboratory in Pharmaceutical Development. EHUO 1st November, 31000 Oran, Algeria

Abstract In pharmacy, Benzoic acid is used as conservative of pharmaceutical preparations and it's classified as notorious effect excipient whose declaration is mandatory in the leaflets and on the packaging of medicines. We synthesized this excipient in Therapeutic laboratory of pharmacy department of Sidi Bel-Abbes according to two different experimental protocols, the first from toluene by oxidation reaction whose yield is low equal to 21.92%, and the second from benzaldehyde by Cannizzaro reaction where we got a better yield equal to 91.02%, four times better.

Keywords Benzoic acid, notorious effect excipient, synthesis, yield

1. Introduction

Benzoic acid is an aromatic carboxylic acid derived from benzene, it's found in the natural state in small quantities. Commercially, benzoic acid E210 is produced by chemical synthesis from toluene. Among the main compounds derived from benzoic acid are salicylic acid and acetylsalicylic acid, known as aspirin [1]. In pharmacy, it's used as a conservative and it's classified as notorious effect excipient whose declaration is mandatory in the leaflets and on the packaging of medicines [1,2]. As side effect, it can cause irritation of skin, eyes and mucous membranes and parenterally, it can increase the risk of jaundice in the newborn [3].

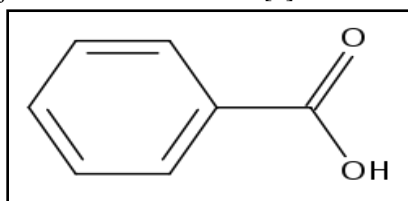


Figure 1: Chemical structure of Benzoic acid [4].

In this study, we compare tow Synthesis methods of Benzoic acid for provides a better yield.

2. Materials and methods

2.1. Synthesis of Benzoic acid by oxidation of toluene

In a 500 ml flask, 150 ml of water and 10 g of potassium permanganate were introduced. After complete dissolution of the potassium permanganate, some pumice stones were added to avoid the risk of explosion and then an ascending condenser was adapted by heating to boiling. 8 ml of toluene was added and then boiled for an hour and a quarter. 10 g of potassium permanganate was added again, boiling another hour and a quarter. Two to three minutes before the reaction was complete, 2 to 4 ml of ethyl alcohol was added to reduce the excess permanganate. On filter



paper, the manganese dioxide formed was filtered and then 20 ml of concentrated hydrochloric acid were added to the filtrate to precipitate the benzoic acid. Finally, the benzoic acid formed was filtered and dried in an oven [5].

2.2. Synthesis of Benzoic acid by Cannizzaro reaction

A three-necked 500 ml was equipped with a separating bulb and a condenser, 35 g of potassium hydroxide was dissolved in 50 ml of water and we proceeded to heating. 40 ml of benzaldehyde was cast rapidly and reflux heating was carried for one hour. Cooling at room temperature was performed. A volume of water necessary for the complete dissolution of the solid phase was added then the solution was transferred to a separating bulb and rinsed with a little water and then with 25 ml of toluene. We decanted and then carried out two extractions on the aqueous phase with 25 ml of toluene [6].

In a beaker, we added to the aqueous solution a concentrated solution of hydrochloric acid up to pH = 1. We cooled it below 10 °C in an ice bath. Filtration and washing with cold water. Finally, the wet crystals of crude benzoic acid were recrystallized from an aqueous solution of ethanol [6].

3. Results and Discussion

3.1. Synthesis of Benzoic acid by oxidation of toluene

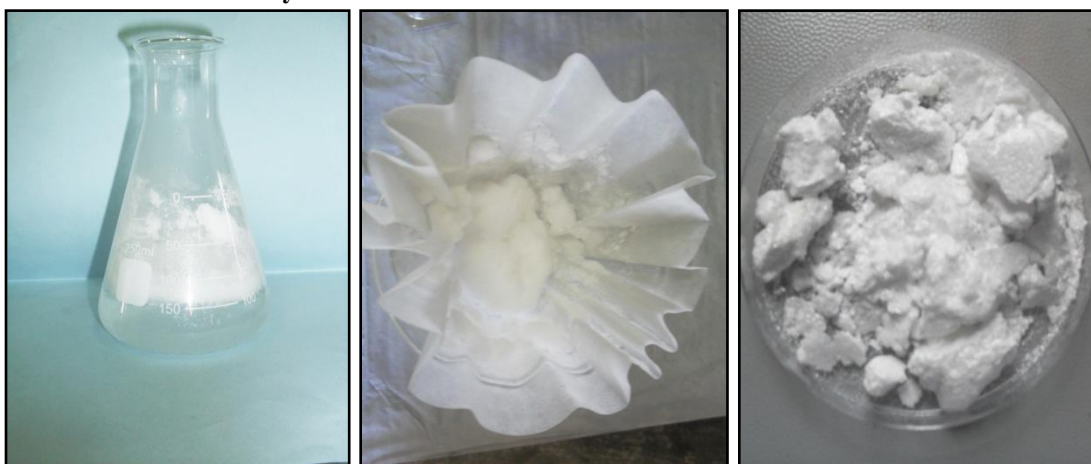


Figure 2: Precipitation, filtration and drying of crystals benzoic acid

The synthesis yield of Benzoic acid by oxidation of toluene is Y: 21.92%.

3.2. Synthesis of Benzoic acid by Cannizzaro reaction



Figure 3: Cooling, settling and extraction

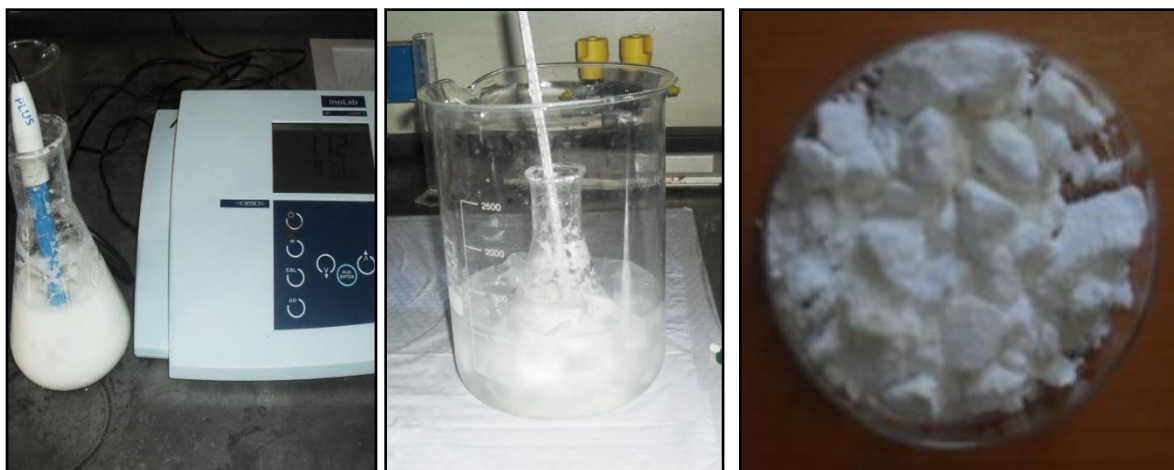


Figure 4: Addition of HCl up to $PH=1$, cooling to $T = 10^{\circ}C$, filtration and drying of benzoic acid crystals

The synthesis yield of Benzoic acid by Cannizzaro reaction is $Y: 91.01\%$.

The synthesis of benzoic acid by the Cannizzaro reaction improved the yield by 69% compared to its synthesis by the oxidation of toluene.

4. Conclusion

The benzoic acid was synthesized according to two different protocols, the first of which was an oxidation of the side chain of toluene with a low yield equal to 21.92%. The second protocol using the Cannizzaro reaction from two molecules of benzaldehyde, one of which is oxidized to benzoic acid with a very satisfactory yield which is equal to 91.02%, four times better than that of the first protocol.

References

- [1]. National Agency for the Safety of Medicines and Health Products. List of Excipients with Notorious Effect. Update of the list and the wordings according to the European Guideline 2003. Second revision of March 3, 2009; 1-84.
- [2]. Excipients and information for notice. Annex to the European Commission guideline on 'Excipients in the labelling and package leaflet of medicinal products for human use'. 2017; 1-22.
- [3]. Concise International Chemical Assessment Document 26. Benzoic acid and sodium benzoate. World Health Organization. 2005; 1-46.
- [4]. European Pharmacopeia 9th edition. Benzoic acid monograph. Chemical structure of Benzoic acid. 2017; 1966-77.
- [5]. Gherib A. Practical work in therapeutic chemistry. 2nd edition. Algiers: Office of University Publications. 1982; 57-61.
- [6]. Jullien A, Beaudoin G J, Flamand E. Experimental organic chemistry. 2nd edition, Berlin. 1997; 691-3.

