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Synthesis of Acetaminophen by Microwave Irradiation Catalyzed on H-Clinoptilolite

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Abstract

The interaction of p-aminophenol with acetic anhydride under microwave irradiation in the presence of H-clinoptilolite was studied during our research on finding economic and ecological methods for the synthesis of acetaminophen (paracetamol). It has been established the effectiveness of the proposed system has been established, which allows the synthesis of the most important drug in a short time with a high yield.

Keywords: Acetaminophen (paracetamol); P-aminophenol; Acetic anhydride; H-clinoptilolite, Microwave irradiation, Thin layer chromatography

Introduction

Previously, we carried out effective the acylation of p-aminaphenol adsorbed from aqueous solutions on H-clinoptilolite. We have carried the same acylation in microwave oven with good yield for obtained desire acetaminophene. In this short communication, we present the results of studying this process by using the found heterogeneous catalytic system in a microwave oven.

Experimental Part

Acetaminophen was synthesized on H-clinoptilolite in a microwave oven. The course of the reaction was monitored using thin-layer chromatography (TLC) on Silufol UV-254.

Microwave irradiation was carried out in a microwave oven "Electronics SP-23 ZIL" (Russia), frequency - 2450MHz. The furnace was equipped with a rectangular waveguide. Gas-liquid chromatography was carried out on a "Cristall-2000M GLC instrument using DB-5" polar liquid phases in the laboratory. Liquid chromatography was carried out on a Shimadzu-Japan apparatus equipped with a diode array detector, NUCLEOSIL 100-5 with a column, C_{18} size 150x4.6mm, sorbent particle diameter 5μm, Mashery-Nagel brand. The liquefaction was carried out according to the isocratic mode. The isolated product was identified by IR (Specord IR-75) and NMR (Varian USA Mercury Plus NMR)1H spectrophotometer (300 MHz), $CDCl_3$ solvent.

The preparation of H-clinoptilolite was carried out according to [1]. The product was identified by joint TLC with starting aminophenol in the previously found effective solvent system - ethyl acetate: hexane 1:1 (R_f of acetaminophen 0.62, R_f of p-aminophenol 0.74) [2].

Synthesis of Paracetamol via Acetylation of p-aminophenol on H-clinoptilolite in a Microwave Oven

2g of H-clinoptilolite was added to a mixture of p-aminophenol (1.1g) and acetic anhydride (1.3ml). The tube was placed in a microwave oven and heated for 2 minutes. The solution was then left for several minutes at room temperature, after which the test tube was immediately placed in a beaker filled with 20ml of cold water (with a few grains of crushed ice) and stirred. After complete separation of the crystals, the reaction mixture was filtered under water vacuum through a Buchner funnel. The filtrate was washed with cold water (8-10°C) and dried on filter paper. Then it was placed in a dryer (100°C). The resulting powder had a light pink color, so it was recrystallized again.

Recrystallization

The formed crystals were dissolved in 70% ethanol solution. Then 25-30ml of the solution was heated to 128 °C, after which it was cooled to room temperature and the flask was refluxed.

The crystallized solution was filtered and dried. After the second crystallization, the crystals turned white [2].

The result was 1.37 grams (0.0091mol) - paracetamol - 91% in 2 minutes. In the absence of a catalyst, 1.21 grams (0.0080mol) were obtained - paracetamol - 80% in 2 minutes.

In the absence of microwave radiation, 1.09 grams of 72% (0.0072mol) were obtained in 1 hour. Product yields are calculated before recrystallization.

The identity of the product was confirmed on a gas-liquid chromatograph with a flame ionization detector under the following conditions: a DB-5 capillary column (polydimethylsiloxane) for GC (0.30m x 25mm), detector FID, N_2 mobile phase, column temperature 100 °C, detector temperature 240 °C, vaporizer temperature 260 °C. Paracetamol retention time 2.40min.

IR spectrum (ν, cm^{-1}) 1660-1560 (arom. ring, C=O, NH), 3325-3150 (NH).

1H PMR spectrum (DMSO-d_6, δ, ppm): 1.9 (s, 3H, CH_3), 6.70 (d, 2H, arom., J 8.2 Hz), 7.65 (d, 2H, arom. J 8.2 Hz), 9.15 (s, 1H, OH), 9.70 (br.s, 1H, NH).

The Discussion of the Results

It should be noted that all reactions were studied in the absence of solvent with a molar ratio of p-aminophenol: acetic anhydride 1:1.2.

Previously, we have shown that p-aminophenol is adsorbed on H-clinoptilolite by the phenolic end, thereby facilitating the nucleophilic addition of the amino group to acetic anhydride. The use of protonated zeolite as a catalyst in this reaction is due to its stability under industrial conditions, selectivity and the presence of heterogenized single catalytic sites. A comparative analysis of the yield and reaction time in the synthesis of acetaminophen by the traditional method and the method using H-clinoptilolite as a heterogeneous catalyst was carried out with a yield of 72% per hour. Microwave acylation of p-aminphenol gives the desired product in 2 minutes in 80% yield. The yield of paracetamol in a microwave oven in the presence of H-clinoptilolite in 2 minutes is 91%. The process of recrystallization of the product from an ethanol solution was carried out until a pure white color of the synthesized acetaminophen was obtained.

Conclusion

The combination of a heterogeneously catalytic method for the synthesis of paracetamol with microwave irradiation of the reaction mixture led to a significant reduction in the reaction time and led to a high yield of the product. In our opinion, all the above mentioned is suitable for optimizing the process under study and increasing the chances of equating the process with green technology.

References

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