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SYNTHESIS OF 4'-AMINOPHENYL BENZIMIDAZOLE

BY

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Abstract. In order to synthesize new azomethines derivate from p-aminophenyl benzimidazole we tried to obtain the benzimidazole using synthetic paths from scientific literature. Three different synthetic methods have been used, the optimal method has been selected and the obtained product was purified by different means in order to establish the best solvent. The samples were analysed by the means NMR spectrometry.

Keywords: p-aminophenyl benzimidazole; different synthetic methods; NMR spectra.

1. Introduction

Benzimidazole moiety is a well-known molecule, also found in natural products such as vitamin B12.

Benzimidazole derivatives are well known and extensively studied, due to their biological activities such as: antidiabetic (Vinodkumar *et al*., 2008), antiviral (Shaida *et al.*, 2009), antioxidant (Kus *et al*., 2008), antihypertensive, (Sharma *et al*., 2010), anti-helmintic (Sawant and Kawade, 2011), antimicrobial (Suthe *et al.*, 2013), anti-inflammatory (Khattab *et al*., 2013; Rajasekaran *et al*., 2012), anti-tumor (Rubbiani *et al*., 2010; Abd El-All *et al.*, 2013; Desai *et al*.,

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1999), anti-spasmotic (Saydin *et al*., 2008), anti-hepatitis C virus (Ishida *et al*., 2006), anti-ulcer (Bharat *et al*., 2008), analgesic (Joseph *et al*., 2010), anti-psychotic (Ingle and Magar, 2011).

Some benzimidazole derivatives have antifungal activity against Candida albicans MTCC 1637, Aspergillus flavus AIIMS and Aspergillus niger AIIMS (Ansari and Lal, 2009).

According to literature data, substitution at 1,2 and 5 position in the benzimidazole ring almost assure that the compound exhibit biological activity. Benzimidazole derivatives, especially those 1N- and 2-substituted are versatile compounds against a large amount of microbes (Ansari and Lal, 2009).

Schiff Bases derived from benzimidazole are also well known for their biological and pharmacological activity, such as: antimicrobial (Naik and Desai, 2004) antifungal (Warad *et al*., 2000) antitumor and anti-inflammatory activity (Chhonker *et al*., 2009).

In this study we present our attempts to obtain p-aminophenyl benzimidazole with a good yield and very pure, so that we could be using it to obtain new Schiff bases with potential biological activity. We also intend to test the activity of those new azomethines.

2. Experimental

2.1. Materials

The NMR spectra were registered on a Brücker WM 400 MHz spectrometer, in DMSO-d6 solution.

All chemicals are of analytical grade, were obtained from commercial sources (Fluka, Merck etc.) and used without further purification. Exception is the o-phenylenediamine that was purified by recrystallization from water.

2.2. Methods

Benzimidazoles can be obtained by an acid catalyzed reaction between aldehydes or ketones and amines (Desai *et al*., 1999; Sawant and Kawade, 2011). New methods of synthesis include microwave irradiation (Varma, 2002), (Abd El-All *et al*., 2013; Khattab *et al*., 2013).

2-(4-Aminophenyl)-benzimidazole has also been obtained by the reaction of o-phenylene diamine with aromatic carboxylic acids in the presence of a strong dehydrating agent – polyphosphotic acid (PPA) or polyphosphotic acid trimethylsilyl ester (Khattab *et al*., 2013). This reaction occurs with high yield.

Benzimidazole can also be obtained by treating o-phenylendiamine with p-aminobenzoic acid using as catalyst o-phosphoric acid yielding 4-(1H-benzo[d] imidazol-2-yl) aniline (Abd El-All *et al*., 2013; Chhonker *et al*., 2009).

According to an American patent 2-(4'amino-phenyl)-5-aminobenzimidazole have been obtained through the condensation of p-nitrobenzoic acid with aniline, followed by the dinitration of the obtained product, reduction of the dinitro derivate to the corresponding triamine and, finally dehydro-cyclisation to the desired product (Condrieu and Saint-Clair-Du-Rhone, 1978).

Due to our raw materials accessibility we choose to apply the second obtaining method.

The condensing reaction occurred using the following general reactions:

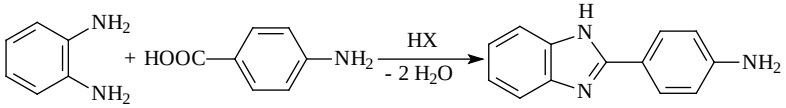

Fig. 1 − Synthesis of p-aminophenyl benzimidazole.

As catalyst three Brönsted acids have been used: HCl, H_2SO_4 and o-phosphoric acid.

Due to the benzimidazole structure at acid pH the amino group is transformed into an ammonium salt. Thus, the neutralization reaction occurs as presented in Fig. 2.

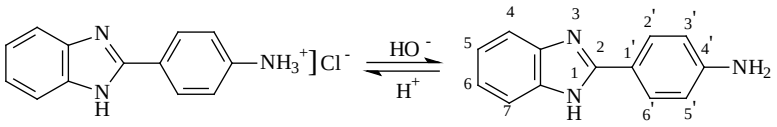

Fig. 2 − Neutralization reaction for benzimidazole derivative.

Synthesis of p-aminophenyl benzimidazole using HCl acid as catalyst. 11 g o-phenylene diamine (0.1 mol) were solved in 40 mL distilled water. 14 g p-aminobenzoic acid (0.1 mol) were also solved in 140 mL 20% solution HCl. The two solutions were mixed and then the reaction flask was heated for 4 h at 120ºC using a reflux condenser. The reaction mixture was cooled, filtered and purified by recrystallization from water and alcohol.

Synthesis of p-aminophenyl benzimidazole using sulfuric acid as catalyst. This method have been described previously in the literature (Kubac *et al*., 2009). Thus, 1.09 g o-phenylene diamine (0.01 mol) and 1.38 g p-aminobenzoic acid (0.01 mol) were added in the reaction flask with 7 mL sulfuric acid 96%. The reaction mixture was heated for 7 h at 165ºC. Next the mixture was cooled to room temperature, diluted with 100 mL distilled water and stirred for 3 h. The benzimidazole derivative was filtered, washed with diluted sulfuric acid, dried and purified by recrystallization from water.

Synthesis of p-aminophenyl benzimidazole using o-phosphoric acid as catalyst. This method has been presented in the literature (Abd El-All *et al*., 2013). So, 1.09 g o-phenylene diamine (0.01 mol) and 1.38 g p-aminobenzoic acid (0.01 mol) were added in the reaction flask with 25 mL o-phosphoric acid. The mixture was refluxed for 4 h and then purred over a mixture of ice and water. Next, 10% solution NH_3 was added to neutralize the pH, using litmus paper as control. The benzimidazole derivative is filtered, washed with cold water and dried. Purification is made by recrystallization from ethanol.

3. Results and Discussions

From all the synthetic methods detailed in the literature we selected the method starting from o-phenylene diamine and p-aminobenzoic acid using HCl as catalyst due to the availability of raw materials, the mild reaction parameters, including reaction time and the high yield presented in literature.

We reproduced exactly the method described and we observed that the reaction mixture was actually a suspension, which means that the reaction occurs very slowly. So we repeated the synthesis and we solved the two reactants separately and then we mixed the two solutions. The reaction mixture was red (comparing to orange in the first case). After 4 h our mixture was a very deep red. We cooled the solution and we initialized the crystallization by rubbing the flask walls with the glass rod. The mixture was left to crystalize overnight. After filtration and washing the precipitate on filter with water we finally obtained 15.3 g raw product with a medium grey colour (the yield in raw product was 60.12% which was acceptable).

The grey amorphous solid was purified by recrystallization from water. In order to adsorb the mechanical impurities, mineral coal was added. For the main product we also made a recrystallization from ethanol. From water we obtained 2.1 g needle crystals off-white colour (the global yield being 8.4%) (sample A). From ethanol white powder separated (sample B).

Because the liquid collected after filtration has a strong acid pH we thought to neutralize it in order to see if we separate more products. After the neutralization with sodium bicarbonate an additional amount of 0.3 g reddish grey solid separated. The crystals were purified by recrystallization from both water (sample C) and ethanol (sample D) (as previously presented).

The 4 samples were then analyzed by NMR spectroscopy in order to identify the products. The obtained spectra are presented in Figs. 3−6.

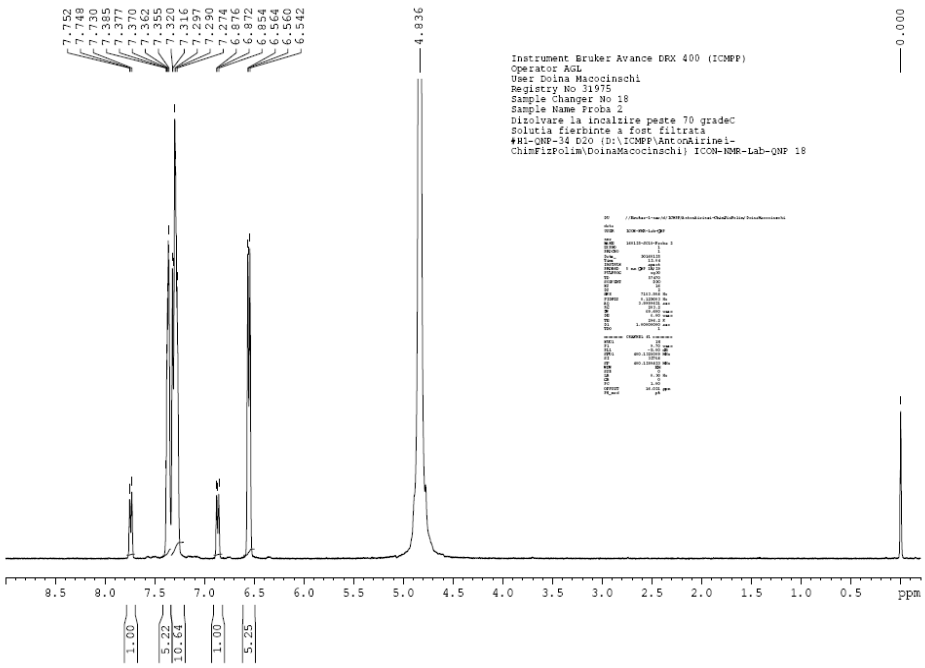

Fig. 3 − NMR spectra for benzimidazole salt purified with water (sample A).

The spectra presented in Fig. 3 is for the p-aminophenyl benzimidazole, the signals being as follows: 4.836 (s, 2H, H3', H5'), 6.542-6.564 (d, 1H, H5), 6.854-6.876 (d, 1H, H6), 7.274-7.297 (d, 1H, H4), 7.316-7.320 (d, 1H, H7), 7.355-7.385 (d, 2H, H2', H6').

So, the purification method is by recrystallization from water and mineral coal is very good, even if we registered a severe drop in the yield.

In Fig. 4, the most prominent peak is that at 2.5 corresponding to the solvent DMSO. From the rest of the peaks is obvious that sample B has a mixture of p-aminobenzoic acid with o-phenylene diamine and small traces of benzimidazole derivative.

So, the purification method using ethanol as solvent is not good in order to separate our product.

From Fig. 5 we deduce that sample C has mainly p-aminobenzoic acid with small traces of benzimidazole and phenylendiamine.

That means that by neutralization we separate mainly the non-transformed raw materials.

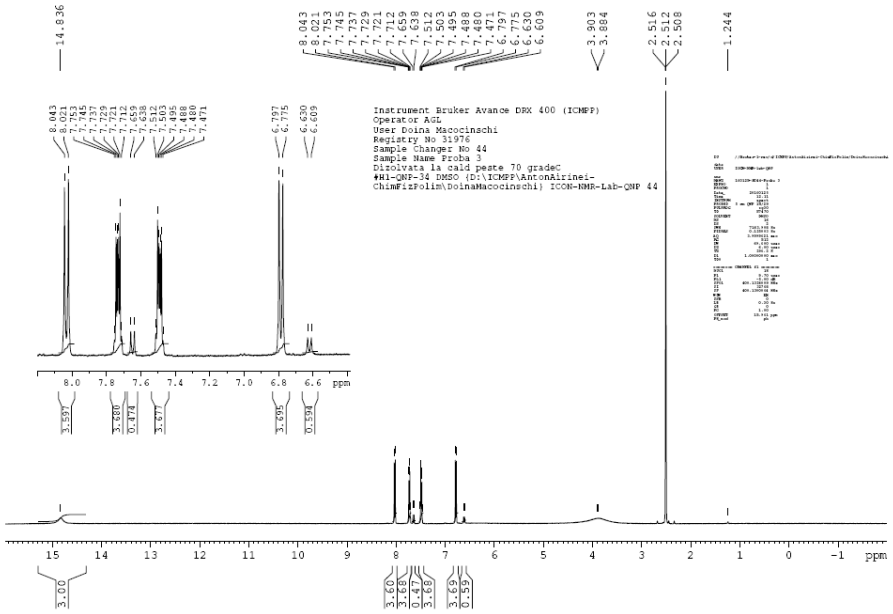

Fig. 4 − NMR spectra for benzimidazole salt purified with ethanol (sample B).

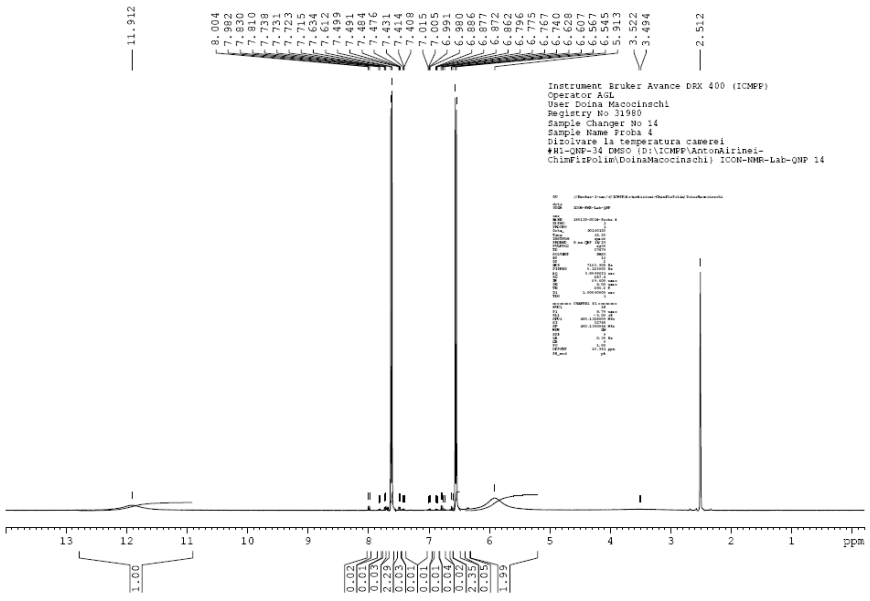

Fig. 5 − NMR spectra for benzimidazole with free amino group purified from water (sample C).

In Fig. 6 we have the spectra for p-aminobenzoic acid, identical with that from the literature. This confirms the previous conclusion that by neutralization we separate the unreacted raw products. Also, by recrystallization from ethanol we purified the aminobenzoic acid from the traces of o-phenylene diamine.

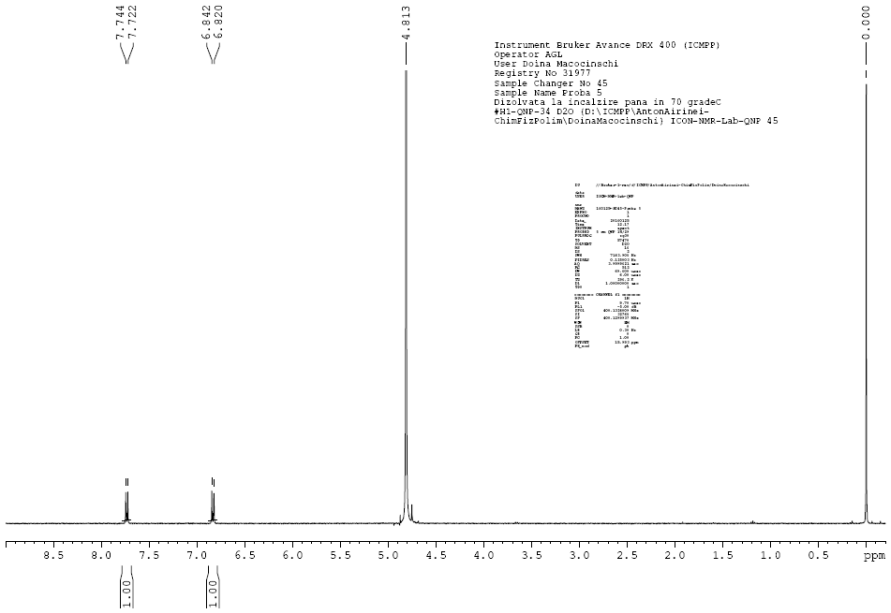

Fig. 6 − NMR spectra for benzimidazole with free amino group purified from ethanol (sample D).

As a general conclusion, this synthetic method occurs with a small yield in the purified product, and in order to separate the phenyl benzimidazole from the raw material a purification from water is required.

Next we tried the synthesis of phenyl benzimidazole using sulfuric acid as catalyst, applying the method found in literature and detailed above. This method has the disadvantage that has a longer reaction time (7 h the main reaction and 3 h for the hydrolysis step) and also the temperature is higher than for the first method. Finally 1.4 g black resinous product has been obtained, thus the yield being 56.6% on raw product. After purification from water and mineral coal 0.3 g beige crystals have been obtained.

Next step we intend to resume this synthesis, using bigger amounts of raw materials and then to analyse the separated product by NMR. Unfortunately, due to the long reaction time this synthetic method is difficult to apply, even if the final product is pure and the yield is 12.14%.

We also tried the synthesis using as catalyst the o-phosphoric acid (method detailed above). We didn't this synthesis because, even if the reaction time is only 4 h (same as for the first method), it requires additional steps that are time consuming. Also, the obtained product is black and resinous in the first step. After neutralizing with 10% ammonia solution, filtration and washing with cold water, a dark brown product has been obtained the yield being very low (under 0.1 g raw product). So, we will not retry this method.

4. Conclusions

Our aim is to obtain new azomethine phenyl benzimidazoles that might have biological properties. In order to do that, the first step is to synthetize p-aminophenyl benzimidazole that will next condense with aromatic aldehydes and obtain the desired Schiff Bases.

So, we tried three different synthetic paths in order to obtain the benzimidazole, each of them having problems of their own. Finally we decided that the first method is the best, despite the low yield. Also, after NMR spectral analysis we decided that the best method of purification is by recrystallization from water with mineral coal.

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SINTEZA 4'-AMINOFENIL BENZIMIDAZOLULUI

(Rezumat)

În scopul obţinerii unor noi azometine plecând de la p-aminofenil benzimidazol am început prin a încerca să sintetizăm derivatul benzimidazolic, aplicând metode de sinteză descrise în literatură. Au fost încercate trei metode de sinteză, am decis care este metoda optimă şi produsul obţinut a fost purificat prin metode diferite pentru a determina solventul optim. Probele au fost analizate prin spectroscopie RMN.