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SYNTHESIS AND CHARACTERIZATION OF NOVEL BENZIMIDAZOLE DERIVATIVES

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ABSTRACT

Benzimidazole and its derivatives are known for their many therapeutic applications and represent one of the most biologically active classes and especially psychotropic activity. They can be used in the conditions of inflammation, microbial infections and also in psychotropic diseases (depression and anxiety). In this way, a new method using Phase-Transfer Catalysis (PTC) by combining families of Benzemidazole and Oxazoline was developed to synthesis two new derivatives. The melting point and Thin Layer Chromatography (TLC) was used verified the purity of the two newly synthesized compounds, then to determine the structure, the analytical techniques of Infrared (IR) spectral studies and Spectroscopy Nuclear Magnetic Resonance (^{1}H NMR) were used. The synthesized compounds will be exposed later to toxicity studies (acute and chronic) and then to psychotropic activity tests in the way to show its psychotropic activities.

KEYWORDS: 2-Mercapto-Benzemidazole, 2-Amino-Benzemidazole, Benzimidazole, Oxazoline, Oxazolidinone, Psychotropic, Phase-Transfer Catalysis, Diethyl-amine.

INTRODUCTION

The appeal of molecules containing heterocyclic ring, results in the fact that these molecules constitute the basic skeleton for a wide variety of compounds with organic, chemical and many pharmacological interest recess.[1, 2] Note that two-thirds of the organic compounds, known in the literature, are heterocyclic[3] and they playing a very important role in the major part of biochemical processes. The highlighting of varied activities of the majority of these molecules encourages researchers to synthesize new series of heterocyclic products.

Heterocyclic structures, whether synthetic or natural, appear as a particularly interesting support in various fields, particularly in the pharmaceutical one. Having attracted considerable interest because of their important biological activities "including the antidepressant and anxiolytic ones".[4, 5] Benzimidazole derivatives and those of Oxazoline was choosing to be studied. The combination of the two molecules in a novel one will be the focus of our work. It involves the synthesis, by the PTC of two novel Benzemidazole derivatives from 2-Mercapro-Benzemidazole and 2-Amino-Benezemidazole, which will have a unit of Oxazolidin-2-one (synthesized by a new method)[6] and also involves the characterization by IR and 1H NMR of the new molecules.

The importance of their pharmacological activities pushes us to assess their toxicity (acute and chronic) and also their psychotropic activity thereafter.

MATERIAL AND METHODS

I. Synthesis

1. Synthesis method

Phase-Transfer Catalysis is now a well-established technique, widely used in synthetic chemistry and applied in many industrial eco-friendly processes.

PTC principle's is based on the transfer of an anionic reagent in the organic phase by forming a pair of lipophilic ion with a lipophilic cation, called Phase-Transfer Catalyst. This technique is applicable to a wide variety of reactions.

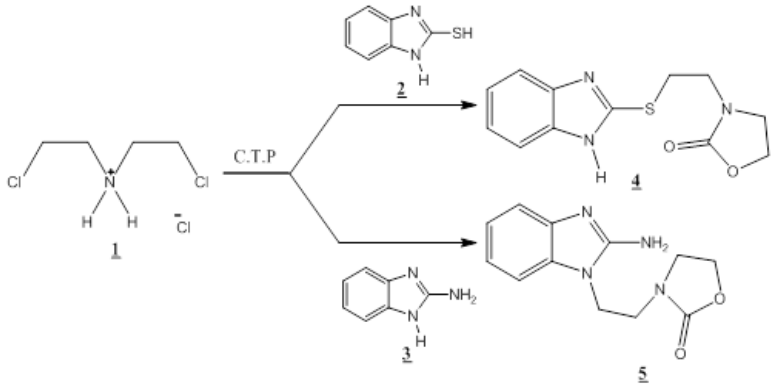
2. Reactions

These two alkylation reactions from two starting products of Benzimidazole, under the same reaction conditions[7,8], to form an Oxazolidin-2-one unit[5,9] whis will be alkylated to Benzimidazole unit. To the solution of Benzimidazole 2 and 3 [shame 1] (1.35 g, 9 mmoles) and Dichloroethyl amine hydrochloride (2.41 g, 13.5 mmoles) in Dimethylformamide (80 ml) were added Potassium carbonate (4.14 g, 30 mmoles) and Tetra-n-butylammonium bromide (0.10 g, 0.3 mmoles).

The resulting mixture was refluxed for 4 h. After filtering the solvent was removed and the residue was purified by column chromatography on silica gel and as mobile phase (Hexane/AcOEt: 60/40) to afford the compound desired.

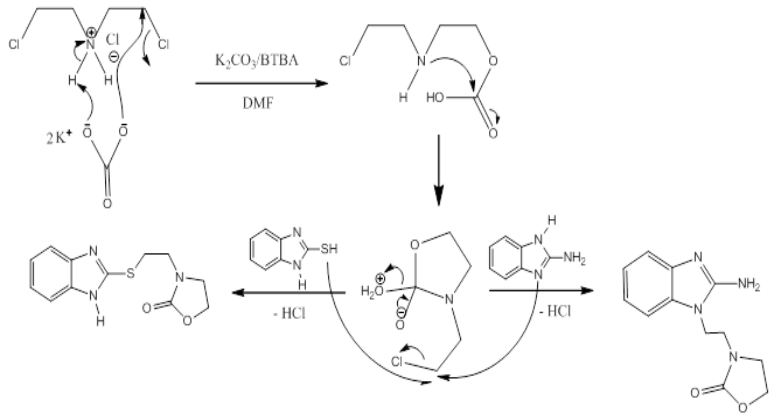
The reaction was carried out for 2-Mercapto-Benzimidazole[10] and redone for the 2-Amino-Benzimidazole.[11,12]

3. Reactions scheme's



Scheme 1: Synthetic route for the preparation of Benzimidazole derivatives.

4. Proposed mechanism scheme



Scheme 2: Representative scheme of the proposed mechanism

II- Characterization

IR, NMR and mass spectra have characterized products obtained from both reactions.

The purity of the two synthesized compounds (4 and 5) were verified by melting point and Thin Layer Chromatography (TLC) and the structure was established following the outcome of analytical techniques of IR spectral and 1H NMR.

RESULTS AND DISCUSSION

I. Results

- **2-mercaptobenzemidazoloxazolin-2-one (4) (Figure1)**

Yield = 70%

F= 230-232°C (Ethanol).

NMR 1H (δ ppm): 3.35: SCH2 (2H. t. J=6.3 Hz); 3.37: NCH2 (4H. m); 4.16: OCH2 (2H. t. J=6.6 Hz); 7.085-7.0116: CH-benzenic (4H. m); 12.54:NH (1H. s)

Mass Spectrum: (IE. M+): m/z=263.

- **2-aminobenzemidazoloxazolin-2-one (5) (Figure 2)**

Yield = 65%

F= 240-245°C (Ethanol).

NMR 1H (δ ppm): 4.144: NCH2 (2H. t. 7.9 Hz); 4.065: NCH2 (2H. t. 6.2 Hz); 6.422: NH2 (2H. S); 6.843-7.135: CH-benzenic (4H. m).

Mass Spectrum: (IE. M+): m/z=246.

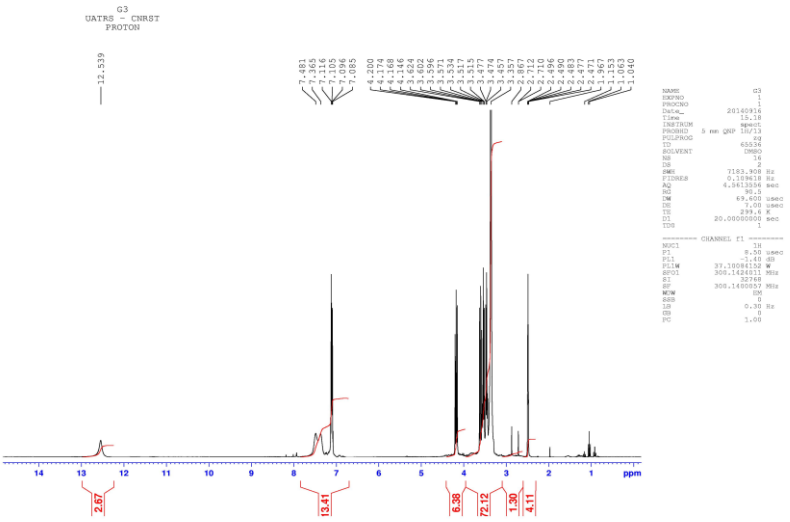


Figure 1: Nuclear magnetic resonance spectrum of 2-mercaptobenzemidazolo-oxazolidinone

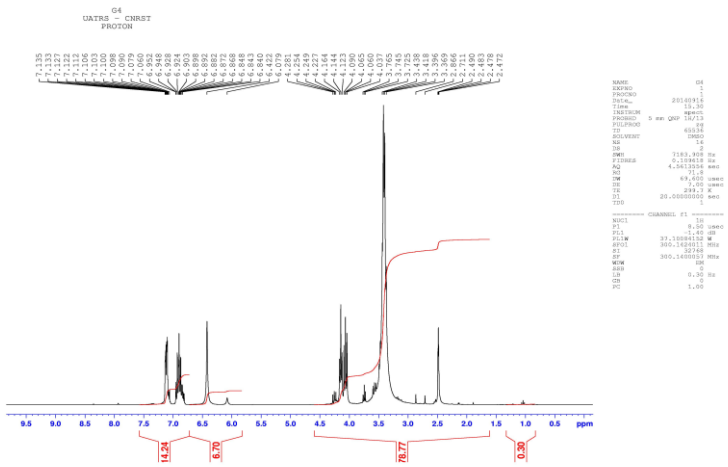
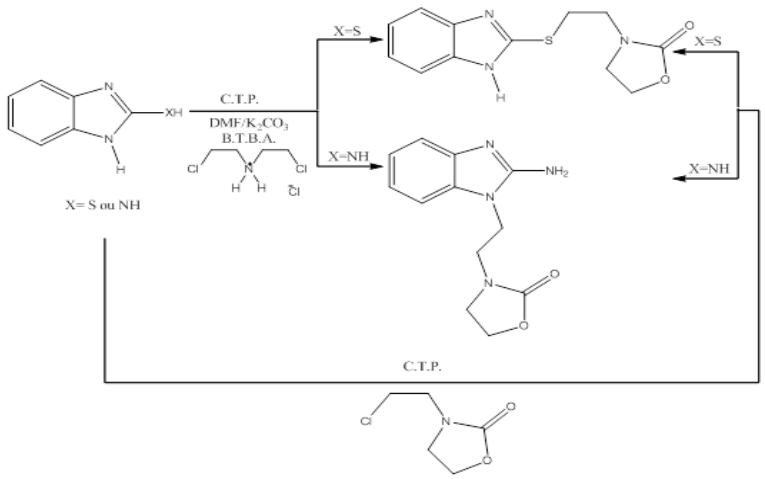


Figure 2: Nuclear magnetic resonance spectrum of 2-aminobenzemidazolo-oxazolidinone

II. DISCUSSION

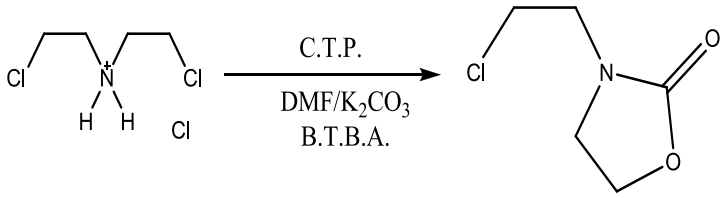
Synthesis by PTC, are giving the expected derivatives in each one of the two reactions. This is the 2-Mercapto-Benzemidazoloxazolin-2-one for the first reaction and 2-Amino-Benzemidazoloxazolin-2-one for the second one. This was confirmed by the results of various tests carried out.

The reaction begins with the formation of the Oxazolidinone unit then it's alkylated with the Benzimidazole unit. This was confirmed by the appearance of an intermediate product[13] on the first hours of the reaction. This was clearly appeared on the chromatography thin layer by a spot wish is different from the spot of starting product and also from the spot of the resulting one. So this is only the Oxazolidinone.



Scheme 3: Reaction steps

This was also confirmed at the reaction of "Dichloroethyl amine chlorohydrate" in PTC conditions, and the "Oxazolidinonne" was given as finale product.



Scheme 4: Illustration of Oxazolidinone unit formation

The results of NMR and mass spectrum confirmed the structure and the composition of the newly synthesized product in each one of the two reactions.

CONCLUSION

Combination of Benzimidazole and Oxazoline has allowed us to have two novel derivatives that have been analyzed by IR, 1H NMR and mass spectra. Assay results were confirmed by obtaining the two expected products and according to the mechanism proposed of a new method of synthesis.

The evaluation of toxicity and biological activity of the products, especially the psychotropic will be the result of our work thereafter.

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