

# Calcined Mussel Shells Doped with Metal Halides as a Novel Catalyst for the Synthesis of Benzimidazoles, Benzoxazoles and Benzothiazoles

Meryem Hamlich<sup>1</sup>, Souad Harkati<sup>1</sup>, Yassine Riadi<sup>3</sup>, Rachid Slimani<sup>2</sup>, Lakhmiri Rajae<sup>4</sup>, Said Lazar<sup>2</sup>, Mohamed Safi<sup>1,\*</sup>

<sup>1</sup>Laboratory of Physical Chemistry and Bioorganic Chemistry, Faculty of Sciences and Techniques, University Hassan II, Mohammedia, Morocco

<sup>2</sup>Laboratory Biochemistry, Environment and Agri-Food, Faculty of Sciences and Techniques, University Hassan II, Mohammedia, Morocco

<sup>3</sup>Department of Pharmaceutical Chemistry, College of Pharmacy, University Sattam Bin Abdulaziz, Alkharj, Saudi Arabia

<sup>4</sup>Laboratory of Materials and Valorization of the Resources, Faculty of Sciences and Techniques, University Abdelmalek Essaadi, Tangier, Morocco

## Email address:

mohamedsafi@yahoo.fr (M. Safi)

\*Corresponding author

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**Abstract:** Calcined Mussel Shells (CMS) doped with  $\text{ZnCl}_2$  are an efficient natural, accessible and reusable catalyst for the synthesis of benzimidazoles, benzoxazoles and benzothiazoles using *o*-phenylenediamine, *o*-aminophenol and *o*-aminothiophenol with different aldehydes. Their actions were conducted under reflux conditions in the air. The procedure is very simple with good to excellent yields in a short reaction time, easy purification. The catalyst can be recycled effectively after used.

**Keywords:** Calcined Mussel Shells (CMS), Heterogeneous Catalysis, Benzimidazoles, Benzoxazoles, Benzothiazoles, Green Chemistry

## 1. Introduction

Over the years, the imidazole nucleus has attracted the attention of the scientific community due to its chemical and biological properties. Imidazole is a planar five-membered heterocyclic ring, highly polar and ionisable aromatic compound. Due to the physiological and pharmacological significance of the imidazole and its derivatives, many scientific researchers have shown much interest in its discovery [1-3].

The benzimidazoles, benzoxazoles and benzothiazoles have also attracted much interest in diverse areas of chemistry [4]. These heterocyclic have different pharmacological properties such as antiviral [5], antimicrobial [6], antifungal [7], antiparkinson [8], anticancer [9], and antibiotic [10]. They are also used as ligands for

asymmetric transformations [11]. As a result of the broad usage of these heterocyclic have been prompted significant efforts toward their synthesis. Several methods have been identified for the synthesis of these heterocyclic (benzimidazoles [12-22], benzoxazoles [23-27], and benzothiazoles [28-32]).

However, many of these methods have one way or the other some setbacks such as drastic reaction conditions, high rate of reaction associated with poor yields, by product formation, demand for toxic reagents and hazardous solvents of expensive catalyst and high demand of excessive oxidative catalysts. Most of these catalysts are homogeneous, non recyclable and coupled with higher temperatures.

Hence, the use of a natural and an environmentally friendly heterogeneous catalyst for the synthesis of benzimidazole, benzothiazole, and benzoxazole are needed.

Mussel shells are considered as ecofriendly catalyst and easily to be obtained at low cost. The calcined mussel shells have higher catalytic activity due to the biogenic calcium carbonate that it contains. In continuation of our research on the application of natural catalysts in organic synthesis [33-37], we have exploited the calcined mussel shells (CMS) as an efficient catalyst for synthesis of benzimidazoles, benzoxazoles and benzothiazoles for the reactions of *o*-phenylenediamine, *o*-aminophenol and *o*-aminothiophenol with different aldehydes.

## 2. Experimental

### 2.1. Preparation and Characterisation of Calcined Mussel Shells (CMS) Catalyst

The mussel shells, named scientifically as *Edulis Mytilus*, were collected from a popular restaurant near Casablanca in Morocco. They were repeatedly washed several times with tap water followed with distilled water and then were dried in an oven at a temperature of 105°C for 12 hours. The dried mussel shells were crushed, powdered to small grains and then calcined at a temperature of 900°C for 2 hours. The residue was washed with distilled water three times and dried at a temperature of 80°C for 24 hours. The residue was finely

chopped and grounded into small particles of different sizes in the range of 100-250  $\mu\text{m}$ , milled in an agate mortar, washed with distilled water, dried overnight at a temperature of 105°C, then calcined at a heating rate of 2°C/min to a temperature of 400°C and maintained at this temperature for 4 hours. The resulting material was stored in a glass bottle for usage without any pretreatment. The prepared calcined mussel shells are denominated (CMS).

### 2.2. Technical Analysis of CMS

The absorbent CMS was characterized using elemental analysis, the FT-IR and XRD. FT-IR spectra were obtained using ATI Mattson Genesis series FTIR<sup>TM</sup> UNICAM instrument. The XRD of the absorbent CMS was carried out by using X pert Pro X-ray diffractometer using copper anticathode  $\lambda(\text{Cu}) = 1.5418 \text{ \AA}$ . The elemental analysis shows a high yield of Ca (60.24%) and Si (3.57%) compared to small amounts of Mg (0.90%), Al (0.41%), P (0.20%) and Sr (0.11%). While the analysis by XRD depicted in (Figure 1) shows the presence of calcite and portlandite syn. The IR spectra analysis of CMS is shown in (Figure 2). The bands at 3643  $\text{cm}^{-1}$  are assigned to hydroxy group stretching modes and folding of carbonate group are assigned to bands at 1437  $\text{cm}^{-1}$  and 874  $\text{cm}^{-1}$ .

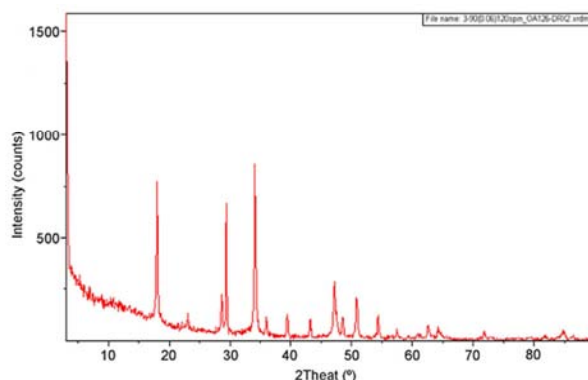


Figure 1. X-Ray diffraction of CMS catalyst.

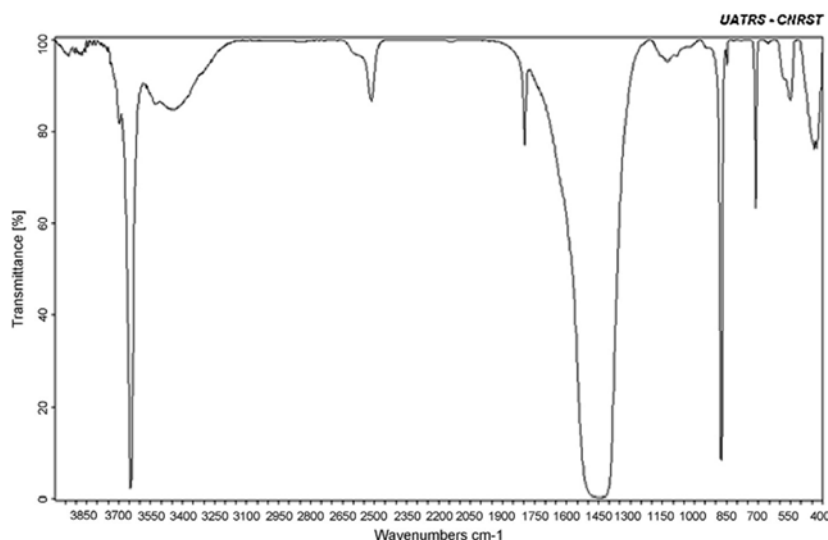


Figure 2. IR spectra of CMS catalyst.

### 2.3. Reaction Procedure

A mixture of *o*-phenylenediamine 1a, *o*-aminophenol 1b or *o*-aminothiophenol 1c (1 mmol), different aromatic aldehydes 2 (1.1 mmol), and a pinch of catalyst (100 mg) in 10 mL toluene were stirred for 10 min and then refluxed at a temperature of 110°C for an adequate time (Table 1) which is determined by TLC (*n*-hexane/EtOAc: 2/1). After the completion of this reaction the catalyst was retrieved from the filtrate, concentrated on a rotatory evaporator and filtered on a silica gel column to make it pure again.

**Table 1.** Optimization for the synthesis of 3a catalyzed by CMS/ZnCl<sub>2</sub>.

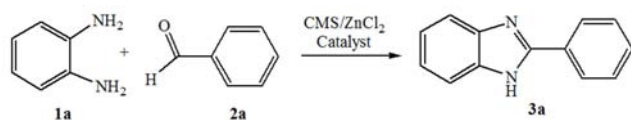
Entry	Solvent	T (°C)	Time	Yield (%) <sup>a</sup>
1	CHCl <sub>3</sub>	50	30min	NR <sup>c</sup>
2	CH <sub>3</sub> OH	25	30min	61
3	CH <sub>3</sub> CN	25	30min	82
4	THF	66	30min	63
5	Water	100	30min	NR <sup>c</sup>
6	Dioxane	100	30min	78
7	Hexane	60	30min	80
8	Ethyl acetate	60	30min	81
9	Free solvent	100	30min	60
10	Toluene	110	15min	41
11	Toluene	110	30min	86
12	Toluene	110	24h	34 <sup>d</sup>
13	Toluene	110	3h	95

<sup>a</sup> Yields in pure isolated products, <sup>c</sup> No Reaction, <sup>d</sup> No catalyst

Hence, the effect of different solvents was studied. The results are summarized in (Table 1).

The effect of various solvents (such as CHCl<sub>3</sub>, CH<sub>3</sub>OH, CH<sub>3</sub>CN, THF, H<sub>2</sub>O, 1,4-dioxane, ethyl acetate and toluene) on this model reaction was observed in the presence of CMS/ZnCl<sub>2</sub>. It was found that some solvents play an important role in this reaction.

Basically, we studied the effect of solvent for the synthesis of benzimidazoles, benzoxazoles and benzothiazoles using CMS/ZnCl<sub>2</sub> as catalyst (Figure 3). The reaction was initially optimized using benzaldehyde 2a and *o*-phenylenediamine 1a, in the presence of CMS/ZnCl<sub>2</sub>, an inexpensive and a readily accessible catalyst. The results are summarized in (Table 1).



**Figure 3.** Synthesis of benzimidazoles 3a catalyzed by CMS/ZnCl<sub>2</sub>.

## 3. Results and Discussion

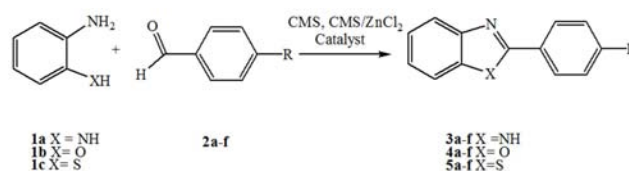
### 3.1. Optimization of the Heterocyclic Construction

Primarily, the reaction between *o*-phenyldiamine 1a and benzaldehyde 2a in the presence of CMS/ZnCl<sub>2</sub> (Figure 3) was selected as a model reaction for the synthesis of benzimidazole to reveal the best solvent for the reaction. The usage of CH<sub>3</sub>OH, THF as solvents gave moderate yields

(Table 1, Entries 2 and 4). In the absence of solvent, significant conversion (Table 1, entry 9) was observed. Without catalyst in refluxing toluene, condensation of benzaldehyde 2a with *o*-phenylene diamine 1a gave low yield and required long reaction times (Table 1, Entry 12). During the use of CHCl<sub>3</sub> (Table 1, Entry 1) as solvent, no condensation was observed regardless of the reaction time. Similar results were observed in the presence of water as solvent (table 1, Entry 5) but good yields were observed with CH<sub>3</sub>CN, Hexane and ethyl acetate (Table 1, Entries 3, 7 and 8). The best conversion was observed when the reaction carried out at a temperature of 110°C using toluene as solvent (Table 1, Entry 11). So this study showed that toluene gave the highest yield (86%) in 30 min compared to the other solvents used in the reaction (table 1).

### 3.2. Extension of the Methodology

For this purpose, a Lewis acid catalyst was prepared by impregnating CMS with ZnCl<sub>2</sub>. The efficiencies of heterocyclic construction were determined using CMS and impregnated CMS analogs (Figure 4).



**Figure 4.** Synthesis of benzimidazoles 3, benzoxazoles 4 and benzothiazoles 5 under CMS, CMS/ZnCl<sub>2</sub>.

In air, a slight excess of aldehyde 2a-f (1.1 equiv.) was used in the presence of amino derivatives 1a-c and CMS catalysts at a temperature of 110°C to build a small collection of fused heterocyclic of type 3-5 (Table 2). The progress of this reaction was monitored by HPLC (C18 column, CH<sub>3</sub>CN /H<sub>2</sub>O 70/30, λ=254 nm, Flow rate: 0.3 mL/mn). After completion of the reaction, the crude product was purified by column chromatography and recrystallization to obtain pure benzimidazoles 3, benzoxazoles 4 and benzothiazoles 5. The physical and spectral characterization of these products was confirmed by comparison with available literature data [37-42].

The results shown on the table below prove that reaction yields increased with CMS/ZnCl<sub>2</sub> compared to CMS. With CMS alone the yield observed is lower with *o*-phenyldiamines (Table 2, Entries 4) when R = OCH<sub>3</sub>, also for *o*-aminothiophenol we noticed that the yields is lower (Table 2, Entries 17) when R = CH<sub>3</sub>. An electro-donating group on aldehyde 2 decreased the efficiency of the heterocyclic building. Reaction yields were between 37 and 94% (Table 2).

After that we studied the results obtained with CMS doped by Lewis acid (ZnCl<sub>2</sub>). It aims to compare the results obtained with that of CMS alone in the same conditions. The products were isolated with moderate to excellent yields (50-98%) (Table 2). Degradation was not observed, and after 3

hours reaction heterocyclic 3-5 were obtained after an easy purification step. We noticed a significantly reduced reaction yields (Table 2, Entry 8) and a small reduction of reaction yields was also observed (Table 2, Entry 12). But in general, we can see the high increase in yield of products when CMS/ZnCl<sub>2</sub> was employed (Table 2).

In brief the conversion obtained with CMS and CMS/ZnCl<sub>2</sub> clearly showed the positive effect of impregnating CMS with ZnCl<sub>2</sub> with few exceptions (Table 2, Entries 8 and 12).

**Table 2.** Synthesis of benzimidazoles 3, benzoxazoles 4 and benzothiazoles 5 under CMS, CMS/ZnCl<sub>2</sub> catalysis.

Entry	Reagent	X	R	Yield % CMS <sup>a</sup>	Yield % CMS/ZnCl <sub>2</sub> <sup>a</sup>
1	3a	NH	H	82%	95%
2	3b		Cl	66%	88%
3	3c		NO <sub>2</sub>	61%	79%
4	3d		OCH <sub>3</sub>	42%	87%
5	3e		CH <sub>3</sub>	76%	89%
6	3f		F	72%	60%
7	4a	O	H	64%	82%
8	4b		Cl	75%	55%
9	4c		NO <sub>2</sub>	73%	98%
10	4d		OCH <sub>3</sub>	75%	97%
11	4e		CH <sub>3</sub>	70%	95%
12	4f		F	94%	80%
13	5a	S	H	77%	98%
14	5b		Cl	66%	87%
15	5c		NO <sub>2</sub>	50%	50%
16	5d		OCH <sub>3</sub>	94%	98%
17	5e		CH <sub>3</sub>	37%	78%
18	5f		F	78%	84%

<sup>a</sup>Yields in pure isolated products, t = 3h, T=110°C.

Due to the reusability of this catalyst, it is very important for large scale or industrial operations. Therefore, the reusability of CMS/ZnCl<sub>2</sub> was studied. The catalyst was separated and reused after been washed with CH<sub>3</sub>CN. The reusability of the catalyst was studied in the model reaction between *o*-phenyldiamine 1a and benzaldehyde 2a in the presence of CMS/ZnCl<sub>2</sub> (Figure 3). The results illustrated in (Table 3) showed that the catalyst can be used three times with a small reduction of its activity; this is due to loss of mass of the catalyst at manipulation.

**Table 3.** Studies on the reuse of CMS/ZnCl<sub>2</sub>.

Entry	Run	Yield % <sup>a</sup>
1	Fresh	95%
2	Recyclage I	90%
3	Recyclage II	89%
4	Recyclage III	88%

<sup>a</sup>Yields in pure isolated products, t = 3h, T=110°C.

## 4. Conclusions

In conclusion, the CMS/ZnCl<sub>2</sub> has shown to be a highly efficient heterogeneous catalyst for the synthesis of benzimidazoles, benzoxazoles, and benzothiazoles from the reaction of various aldehydes with *o*-phenylenediamine, *o*-

aminophenol or *o*-aminothiophenol with remarkable results. This catalyst is natural, accessible, ecofriendly, inexpensive and recycled. Furthermore, CMS/ZnCl<sub>2</sub> as a catalyst for this reaction helps to have high yields of products, easy work-up and other considerable advantage.

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