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New Methodologie Eco-Friendly Using Calcined Eggshell Meal Catalyst for Synthesis of Benzimidazoles, Benzoxazoles and Benzothiazoles

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Abstract: The Calcined Eggshell Meal (CEM) doped is a new solid support has been employed as a catalyst for efficient synthesis of benzimidazoles, benzoxazoles and benzothiazoles. Taking into account environmental and economical considerations, the handling of CEM used here presents many advantages such as simple and convenient procedure, easy purification and shorter reaction time and enhanced recycling possibilities, which are now well established in fine organic synthesis.

Keywords: Calcined Eggshell Meal, Heterogeneous Catalysis, Benzimidazoles, Benzoxazoles, Benzothiazoles, Recyclable Catalyst

1. Introduction

The benzimidazoles, benzoxazoles and benzothiazoles structural motifs play very important roles in numerous pharmaceutical molecules with a wide range of biological properties including antibacterial [1], antibiotic [2], anticonvulsant [3], anticancer [4], antihypertensive [5], antifungal [6], anti-inflammatory [7], immunosuppressant agents [8] and antiviral effects [9]. Consequently, the synthesis of the heterocyclic nucleus has gained great importance. Many methods for the synthesis of benzimidazoles [10-19], benzoxazoles [20-24] and benzothiazoles [25-29] have been discovered and reported.

However, all of these procedures suffer from one or more of the following disadvantages such as long reaction times, low yields of the products, harsh reaction conditions, the use of excess amounts of reagents, tedious workup procedures, and co-occurrence of several side reactions. In addition, some of the catalysts and reagents are expensive, toxic, and air sensitive. Therefore, there is still a need to search for better catalysts that could be superior to the existing ones with regards to toxicity, handling and operational simplicity.

Nowadays, many organic reactions have been devised in such a way that the reagents are deposited on various inorganic solid supports. These reagents are becoming a major area of chemical research due to the wide variety of organic transformation that can be carried out under mild experimental conditions and the continuing drive for cleaner and more efficient processes [30].

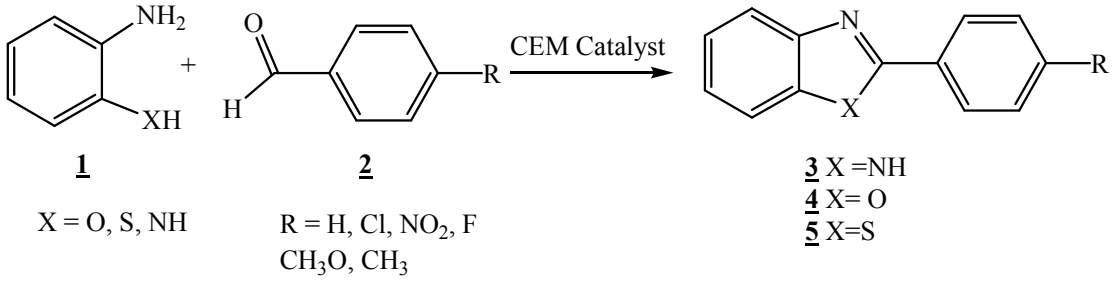
For our own part, we recently reported that Animal Bone Meal (ABM), a source of biogenic apatite and a cost-effective material, could be used as catalyst in several reactions [31].

Eggshell Meal represents a source of biogenic calcium carbonate. Considering good catalytic properties of synthetic calcium carbonate powder towards organic synthesis, the main aim of this study was to evaluate Calcined Eggshell

Meal (CEM) as original heterogeneous catalyst in organic synthesis. The natural support CEM has employed as catalyst in Knoevanegel reaction [33].

A brief and easy method to prepare the CEM as catalyst in synthesis of benzimidazoles, benzoxazoles and benzothiazoles has been developed. As far as we know, it is the first report of the use of this natural source to perform organic reactions with low cost and high efficiency.

In continuation of our effort to explore the catalytic activity of CEM for useful organic transformation we herein report that Lewis acids doped CEM catalyzed a simple and environmentally benign synthesis of benzimidazoles, benzoxazoles and benzothiazoles, from the reaction of *o*-phenylenediamine, *o*-aminophenol and *o*-aminothiophenol with different aldehydes (Scheme 1).



Scheme 1. *Synthesis of benzimidazoles 3, benzoxazoles 4 and benzothiazoles 5 catalyzed by CEM, $ZnCl_2$/CEM and $CuBr_2$/CEM.*

2. Experimental

2.1. Preparation and Characterisation of CEM Catalyst

Eggshells were collected, then washed several times with tap water and left in open air for several days to get rid of odours. Later, they were transferred to the oven at 80°C for drying. The dried Eggshells were crushed and milled into different particle sizes in the range 45-200 µm, calcined at 800°C for 2h. The residue was washed with water and was used after drying 24h at 80°C. The residue was washed with water and was dried overnight at 100°C in a conventional draying oven and then calcined at a heating rate of 2°C/min to 400°C and kept at this temperature for 4h. The resulting material was denominated CEM.

The chemical composition of CEM shows a high yield of Ca (61.95%) compared to small amounts of Mg (0.79%), Si (0.65%), Na (0.64%), P (0.47%), Al (0.17%) and Cl (0.12%). The X-ray diffraction of our Catalyst is shown in Figure 1 show a main peak appeared at 2θ=34.13°. In addition, this spectrum shows several other small peaks at 2θ = 18.07°, 23.08°, 28.72°, 29.43°, 36.03°, 39.47°, 48.55°, 50.85°, 57.48°, 60.74°, 62.62°, 64.30°, 71.80° and 81.88°. This spectrum confirms the presence of calcite, syn and portlandite. Analysis of FT-IR spectrum of CEM gave some bands at 3600 cm^{-1} that are assigned to -OH stretching modes and the stretching and folding of carbonate group has been assigned to peaks at 1500 cm^{-1} and 865 cm^{-1}. The specific surface area of the CEM calculated by the BET (Brunauer-Emmett-Teller) method is 62.42 m^2/g.

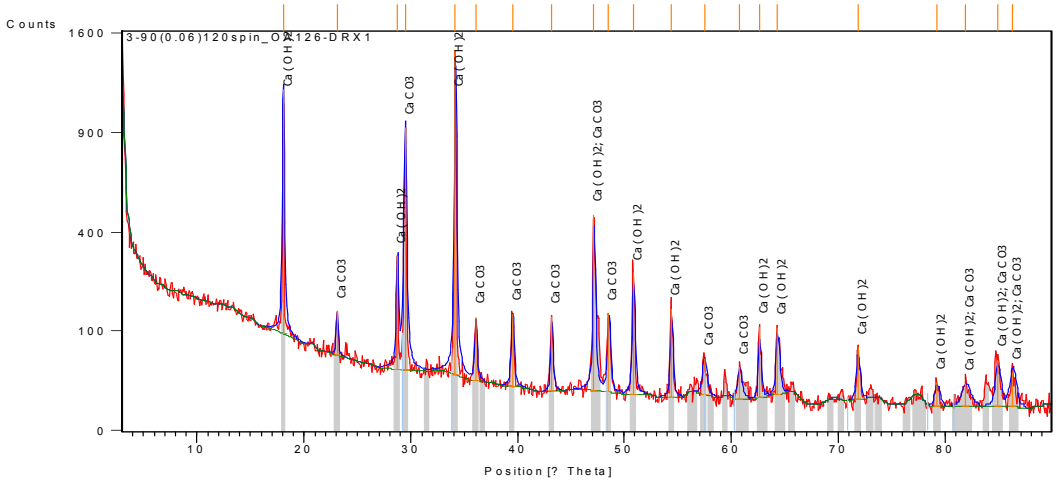


Figure 1. *X-ray diffraction of CEM.*

2.2. Reaction Procedure

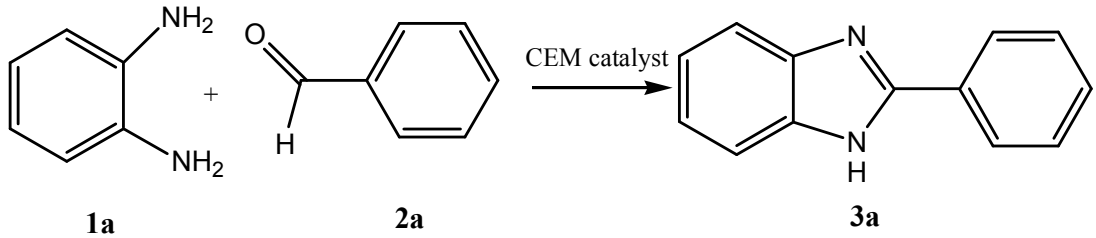
A mixture of *o*-phenylenediamine 1a, *o*-aminophenol 1b or *o*-aminothiophenol 1c (1mmol), different aromatic aldehydes 2 (1,1mmol), and a pinch of catalyst (100mg) in 10mL toluene were stirred for 10min and refluxed further at 110°C for an appropriate time (Table 1) which was monitored by TLC (*n*-hexane/EtOAc : 2/1) and HPLC. After completion of

the reaction, catalyst was recovered from the filtrate, concentrated on a rotatory evaporator and chromatographed on a silica gel column to offer pure product.

3. Results and Discussion

3.1. Optimization of the Heterocyclic Construction

In the initial experiment, we investigated various conditions in the model reaction of *o*-phenylenediamine 1a with benzaldehyde 2a in the presence of CEM/$ZnCl_2$ (Scheme 2) and the results were summarized in Table 1.



1a **2a** **3a**

Scheme 2. *Synthesis of benzimidazoles 3a catalyzed by $ZnCl_2$/CEM.*

The effect of various solvents (such as $CHCl_3$, CH_3OH, CH_3CN, THF, H_2O, 1,4-dioxane and toluene) on the model reaction was conducted in the presence of CEM/$ZnCl_2$. The result indicated that the solvents had a significant effect on the product yield. The use of, $CHCl_3$, CH_3CN and 1,4-dioxane as solvent gave moderate yields (Table 1, Entries 1, 3 and 6), The use H_2O as solvent gave no reaction(Entry 5), but the good yields was observed with THF and free solvent (Entries 4, 13). The best conversion was observed when the reaction was performed in toluene at 110°C (Entry 10). A mixture of starting materials and final heterocyclic was obtained. The best solvent remains toluene, but it should be pointed out that heterocyclic construction also requires thermal, aprotic and apolar conditions.

Without catalyst in refluxing toluene, condensation of benzaldehyde 2a with *o*-phenylenediamine 1agave low yield and required long reaction times (Entry 12). No condensation was observed in the absence of air [33] prevents the required oxidative step and benzimidazole were not detected (Entry11).

In air and in the presence of $ZnCl_2$/CEM, reactions between 2a and *o*-phenylenediamine furnished the desired cycloadducts 3a after 3h in good to excellent yields (Entries 8,9,10). In addition, temperature and time play a role, reactions performed in refluxing toluene showed a better efficiency.

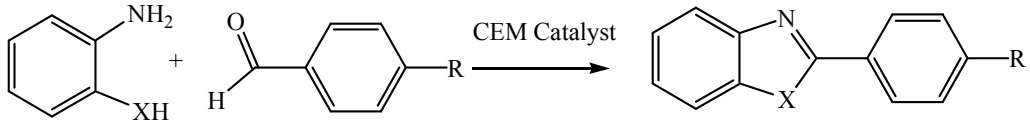
Table 1. *Optimization for the synthesis of 3a catalyzed by $ZnCl_2$/CEM.*

Entry	Solvent	T (C°)	Time(h)	Yield (%)[a]
1	$CHCl_3$	50	3h	61
2	CH_3OH	25	3h	83
3	CH_3CN	25	3h	49
4	THF	66	3h	81
5	Water	100	3h	NR[c]
6	Dioxane	100	3h	61
7	Toluene	70	3h	26
8	Toluene	100	3h	76
9	Toluene	110	2h	78
10	Toluene	110	3h	96
11[b]	Toluene	110	24h	NR[c]
12	Toluene	110	24h	34[d]
13	free	100	3h	80

[a] Yields in pure isolated products; [b] No Air;[c] No Reaction; [d] No catalyst.

3.2. Extension of the Methodology

For these purpose, two other Lewis acid catalysts were prepared by impregnating CEM with $ZnCl_2$ or $CuBr_2$. Heterocyclic construction efficiency was also performed using CEM alone and doped CEM analogs.



1a X = NH
1b X= O
1c X=S

2a-f

3a-f X =NH
4a-f X= O
5a-f X=S

Scheme 3. *Synthesis of benzimidazoles 3, benzoxazoles 4 and benzothiazoles 5 under CEM, CEM/$ZnCl_2$ and CEM/$CuBr_2$.*

In air, a slight excess of aldehyde 2a-f (1.1 equiv.) was used in the presence of amino derivatives 1a-c and CEM catalysts at 110°C to build a small library of fused heterocyclic of type 3-5 (Table 2). Reaction progress was monitored by HPLC (C18, CH_3CN /H_20 70/30, λ=254 nm, Flow rate : 0,3mL/mn). After completion of the reaction, the crude product was purified by column chromatography and recrystallization to afford pure benzimidazoles 3, benzoxazoles 4 and benzothiazoles 5. Physical and spectral characterization of the products was confirmed by comparison with available literature data [31, 33-37].

With CEM alone, the reaction proceeded smoothly throughout heterocyclic construction and the yield was lower (Table 2, Entries 9, 10). An electro-donating group on

aldehyde 2 decreased the efficiency of the heterocyclic building. Reaction yields were between 9 and 94% (Table 2).

Under similar conditions, the use of CEM doped with MX_2 Lewis acids the products were isolated in moderate to excellent yields (52-98%). Degradation was not observed and after 3h, heterocyclic 3-5 were obtained after an easy purification step. Reaction yields and speed slightly decreased when methoxy or methyl benzaldehydes 2d and 2e (Entries 4-5, 10-11 and 16-17) were employed. The conversion obtained with CEM, $ZnCl_2$/CEM and $CuBr_2$/CEM clearly showed the positive effect of the impregnating process $ZnCl_2$ doped CEM.

Table 2. *Synthesis of benzimidazoles 3, benzoxazoles 4 and benzothiazoles 5 under CEM, $ZnCl_2$/CEM, and $CuBr_2$/CEM catalysis.*

Entry	Reagent	X	R	Yield %, CEM	Yield % $ZnCl_2$/CEM	Yield % $CuBr_2$/ CEM
1	3a	NH	H	86%	94%	55%
2	3b		Cl	79%	85%	44%
3	3c		NO_2	90%	65%	82%
4	3d		OCH_3	46%	84%	47%
5	3e		CH_3	81%	98%	96%
6	3f		F	46%	53%	82%
7	4a	O	H	50%	52%	52%
8	4b		Cl	94%	67%	66%
9	4c		NO_2	32%	76%	39%
10	4d		OCH_3	9%	59%	80%
11	4e		CH_3	72%	62%	72%
12	4f		F	84%	87%	48%
13	5a	S	H	90%	93%	93%
14	5b		Cl	90%	95%	97%
15	5c		NO_2	20%	54%	58%
16	5d		OCH_3	90%	66%	82%
17	5e		CH_3	92%	66%	98%
18	5f		F	90%	92%	94%

[a] Yields in pure isolated products; t = 3h; T= 110°C.

The recycling performance of the CEM/$ZnCl_2$ in the model reaction was also investigated. After completion of the reaction, the isolated CEM/$ZnCl_2$ was washed with CH_2Cl_2 and reactivated at 400°C for 2h, and can be reused for times, after for recycles the catalytic activity of CEM/$ZnCl_2$ was almost the same as that of fresh catalyst (Table 3). Catalytic processes and reduced environmental problems (lower energy, valorization of waste as natural and reusable catalyst, non toxicity of the catalyst, reduced amount of solvent).

Table 3. *Studies on the reuse of CEM/$ZnCl_2$.*

Entry	Run	Yield % 3a
1	fresh	99 %
2	Recycle I	96 %
3	Recycle II	95 %
4	Recycle III	92%
5	Recycle IV	91 %

[a] Each reaction was carried out as described in reference [36]

4. Conclusion

In summary, we have developed a simple and efficient one-pot synthetic approach for the synthesis of benzimidazoles, benzoxazoles and benzothiazoles by the condensation of various *o*-phenylenediamine, *o*-aminophenol or *o*-aminothiophenol and aromatic aldehydes in the presence of CEM/$ZnCl_2$. This methodology offers very attractive features such as reduced reaction times, high yields and atom efficiency, as well as easy product separation. The operational simplicity of the procedure is also attractive from the green chemistry point of view.

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