

KO9 as an efficient catalyst for the synthesis of benzimidazoles and benzothiazoles

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Abstract— In this work we describe a simple and efficient procedure for the synthesis of 2-aryl-benzimidazoles (2-aryl-benzothiazoles) by condensation of o-phenylenediamine (or 2-aminobenzothiazole) with aryl aldehydes using natural phosphate (K09) as a catalyst in methanol. Little reaction time, the large-scale synthesis, easy and quick isolation of the product, and excellent performance are the main advantages of this procedure.

Index Terms— Natural phosphate, Heterogeneous catalysis, Benzimidazoles, methanol, use

1 INTRODUCTION

The benzimidazole and benzothiazole skeletons can be found in numerous pharmaceutical agents having a varied spectrum of biological properties [1-4]. They present antiviral, antiulcer, antihypertensive and anticancer activities [5]. Benzimidazoles are biologically effective [6] and this fragment is an important pharmacophore [7] in the discovery of drugs and also a good intermediate [8] for the synthesis of many important organic compounds. In general, the traditional synthesis of benzimidazoles comprises the condensation of o-phenylenediamine with the carboxylic acid or their derivatives [9] (nitriles, imidates, or orthoesters) [10] under strongly acidic conditions and sometimes associated with Very high temperatures or microwave irradiation [11]. These derivatives often generated from the condensation of o-phenylenediamines with aldehydes [12] under oxidizing conditions [13,14] using various oxidative and catalytic reagents, such as nitrobenzene [15], Zn-proline [16], H_2O_2 / HCl [17], $Na_2S_2O_5$ [18], $FeCl_3 \cdot 6H_2O$ [19], Benzofuroxane [20], MnO_2 [21], $Pb(OAc)_2$ [14], $KHSO_4$ [22], (bromo dimethyl) sulfonium bromide [23], p-TSA [24], $ZrOCl_2 \cdot 8H_2O$ [25], $ZrCl_4$ [26], $HfCl_4$ [26], boron trifluoride [27] and copper iodide catalysts [28] were used as reagents or catalysts for the synthesis of benzimidazoles.

Although the reaction has been effectively promoted by the above conditions, they are often homogeneous catalysts and some of these methods suffer from one disadvantage or another, such as the use of hazardous and carcinogenic solvents, high catalyst loading, the difficulty of separating the products from the reaction mixture or catalysts which sometimes contain toxic metals.

Therefore, the discovery of light and practical heterogeneous catalysts, stable, inexpensive, recyclable and environmentally friendly for the synthesis of 2-substituted benzimidazoles

continues to attract the attention of researchers.

The phosphate compound is an environmentally friendly solid material with excellent mechanical strength and stability.

Here, we would like to mention our work on natural phosphate (K09) to catalyze the synthesis reaction of the benzimidazole and benzothiazole derivatives with great efficiency and excellent reusability. The catalyst can be readily recovered and still retains its catalytic activity.

We have shown that K09 could be considered as a new heterogeneous catalyst for the synthesis of benzimidazole and benzothiazole derivatives.

2 MATERIEL ET METHODS

✓ General information for the catalyst

The commercial grade natural phosphate K09 is taken as a basic precursor in the preparation of the catalysts. A sample of the natural phosphate was subjected to a treatment consisting of washing with water followed by preliminary sieving to remove the impurities associated with the phosphate minerals. After this operation, the grinding is carried out with sieving which makes it possible to retain that the granulometry of the phosphate at an area between 63 and 125 μm . The phosphate thus obtained is preserved and dried at 100°C in the oven.

The natural phosphate samples thus treated were then characterized by IR spectroscopy, X-ray diffraction analysis (XRD), Energy Dispersion Spectroscopy (EDS) and by Measurement of the specific surface area.

Analysis by IR spectroscopy shows several bands, in particular those attributable to PO_4^{3-} and carbonate ions CO_3^{2-} (Figure 1). The absorption bands of the groups PO_4^{3-} are in the range between 1100 and 950 cm^{-1} and between 571 and 601 cm^{-1} . We have also identified the adsorption bands characteristic of carbonates at 1458, 1430 and 870 cm^{-1} . The IR spectrum has no absorption band characteristic of the hydroxyl ions OH at 3560 and 630 cm^{-1} , which confirms that this phosphate is a carbonated fluoroapatite [29-31].

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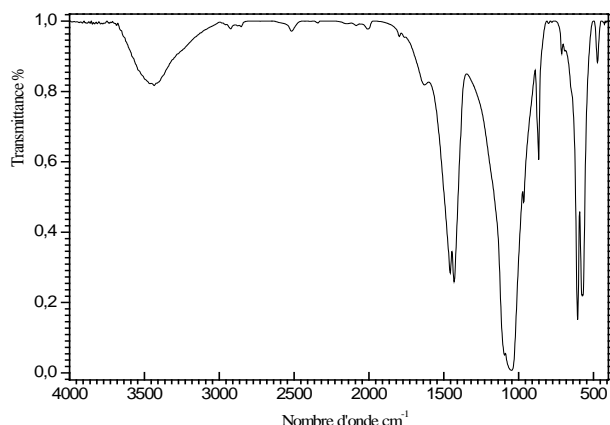


Figure 1: IR absorption spectrum of naturel phosphate K09.

The purpose of X-ray diffraction analysis (XRD) is to determine the phases and the state of crystallization of the materials by means of the position and the intensities of the diffraction peaks. Compounds were identified by comparing with the Joint Committee on Powder Diffraction Standards cards in the conventional way [32]. The diffractogram of the sample (Figure 2) shows that the principal minerals found are the francolite (2θ : 31.91°; 25.89°; 34.14; 28.18), quartz, SiO_2 and calcite CaCO_3 [33-35].

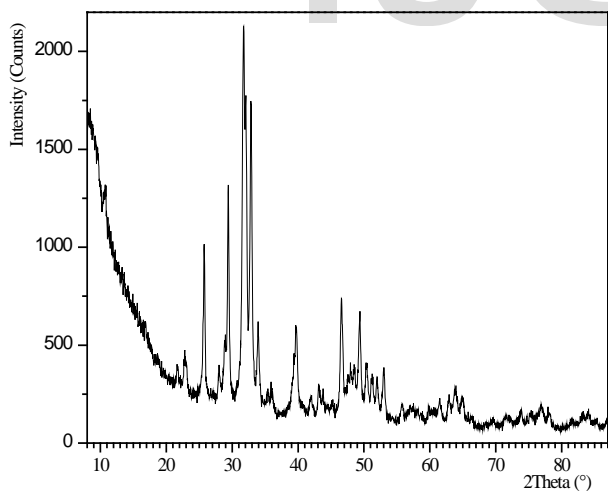


Figure 2: Diffractogram of naturel phosphate K09.

The elemental composition of the same samples was determined by Energy Dispersion Spectroscopy (EDS) with an EDAX spectrometer. The table (Table 1) below gives the mine-

ralogical composition of the phosphates used in this study. This natural phosphate consists mainly of calcium and phosphate ions and several minor elements. Among these elements are Si, Na, K, Al, S, Mg, Cd, Cr and Fe. The Ca / P molar ratio is of the order of 2.13, slightly higher than that of a stoichiometric phosphocalcic apatite (Ca / P = 1.667). This difference in ratio is related to the presence of calcium carbonate and other impurities as we have detected by infrared spectroscopy and by X-ray diffraction. All these results of physico-chemical analysis confirm that the phosphate is a carbonated fluorapatite-Froncolite [36].

The surface area of the K_{09} was determined by the Brunauer, Emmet and Teller (BET) nitrogen adsorption method. Its

TABLE 1
MINERALOGICAL COMPOSITION OF NATURAL PHOSPHATE K09.

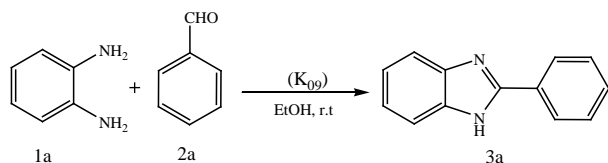
| compound | Concentration% |
|-------------------------|----------------|
| CaO | 43,6 |
| P_2O_5 | 33,5 |
| F | 5,95 |
| SiO_2 | 2,99 |
| SO_3 | 2,21 |
| Na_2O | 1,23 |
| Al_2O_3 | 0,825 |
| MgO | 0,497 |
| Fe_2O_3 | 0,237 |
| SrO | 0,116 |
| K_2O | 0,0704 |
| Cl | 0,0655 |
| Y_2O_3 | 0,0351 |
| ZnO | 0,0344 |
| I | 0,0197 |
| U_3O_8 | 0,0195 |

specific surface is 13.8 m^2/g .

3 RESULTS AND DISCUSSION

3.1. Evaluation of the catalytic activity of K09 in the synthesis of benzimidazole

Initial studies were realized with the 1,2-phénylènediamine **1a** and of the benzaldéhyde **2a** as reaction models (Scheme 1). The reaction was made in 25 ° C with a different mass of catalyst. The best result was obtained with an amount of 0.05 g of the catalyst in terms of reaction time and isolated yield (Table 1, entry 6). When the content in catalyst was increased to 0.2 g, the product yield decreased to 56% (Table 2, entry 8). In addition, the blank test was also performed under identical reaction conditions, and it has given the product in a yield of 12% after 16 hours (Table 2, entry 1). These results indicate that the catalyst used present a high catalytic activity in this transformation.



Scheme 1 : Reaction of synthesis of benzimidazoles between the 1,2-phénylènediamine and benzaldéhyde

TABLE 2
EFFECT OF THE MASS OF K09 ON THE CONDENSATION BETWEEN **1a** AND **2a**.^a

| Entry | Catalyst (g) | Times (h) | Yield (%) ^b |
|-------|--------------|-----------|------------------------|
| 1 | - | 16 | 12 |
| 2 | 0,01 | 1 | 44 |
| 3 | 0,02 | 1 | 51 |
| 4 | 0,03 | 1 | 66 |
| 5 | 0,04 | 1 | 74 |
| 6 | 0,05 | 1 | 78 |
| 7 | 0,1 | 1 | 72 |
| 8 | 0,2 | 1 | 56 |

^a Reaction conditions: **1a** (1 mmol), **2a** (1 mmol), catalyst, EtOH (3 mL), r.t. for 60 mn.

^b Isolated yield.

3.2. The solvent effect

The effect of various solvents (such as MeOH, EtOH, EtOAc, CH₂Cl₂, CH₃CN, THF, CHCl₃, and 1,4-dioxane) on the model reaction was performed in the presence of K09. The results indicate that the solvents had a significant effect on the yield of the product. The use of dioxane, EtOAc and CHCl₃ as a solvent gave low yields (Table 3, entry 5, 7 and 10). Solvents such as CH₃CN, THF and CH₂Cl₂ gave moderate yields (Table 3, entries 6, 8 and 9). The best conversion was observed when the reaction was performed in methanol (Table 3, entry 3). Based on these results, the MeOH was then selected as a solvent for other investigations.

3.3. The effect of the reaction time

To study the effect of the reaction time (Table 4) we chose the mass 0.05g as optimum mass in the presence of MeOH as solvent. The reaction mixture in MeOH with 0.05 g of a mass of K09 at room temperature for a short time of the reaction gave 86% by 3a (Table 4, entry 5). However, when the reaction time was increased, the yield of 3a started to increase. The compound 3a was obtained in a yield of 86% at room temperature, after 30 mn of reaction.

TABLE 3
EFFECT OF DIFFERENT SOLVENTS ON THE SYNTHESIS OF 2-PHENYL-1H-BENZIMIDAZOLE CATALYZED BY K09.^a

| Entry | Solvents | Times (h) | Yield (%) ^b |
|-------|---------------------------------|-----------|------------------------|
| 1 | - | 1 | 30 |
| 2 | EtOH | 1 | 78 |
| 3 | MeOH | 1 | 82 |
| 4 | H ₂ O | 1 | 61 |
| 5 | Dioxane | 1 | 34 |
| 6 | CH ₃ CN | 1 | 56 |
| 7 | AcOEt | 1 | 44 |
| 8 | THF | 1 | 53 |
| 9 | CH ₂ Cl ₂ | 1 | 56 |
| 10 | CHCl ₃ | 1 | 32 |

^a Reaction conditions: benzaldéhyde (1 mmol), 1,2-phénylènediamine (1 mmol), 0.05 g catalyst, solvant (3 mL), r.t. for 60 mn.

^b Isolated yield.

3.4. The effect of reaction temperature

The temperature also plays an important role in organic synthesis, due to its effects on the reaction rate. Thus, a study of the effect of temperature (Table 4) was examined. It was found that the activity of the synthetic reaction of benzimidazole in the presence of K09 can be increased by raising the temperature to achieve the best yield from 90% to reflux after only 15 mn (Table 4, entry 9). Based on the screening temperature, we chose the reflux, as the optimum temperature for the reaction of synthesis of benzimidazoles.

TABLE 4
EFFECT OF DIFFERENT SOLVENTS ON THE SYNTHESIS OF 2-PHENYL-1H-BENZIMIDAZOLE CATALYZED BY K09.^a

| Entry | Times (mn) | Temperature (°C) | Yield (%) ^b |
|-------|------------|------------------|------------------------|
| 1 | 3 | r.t | 12 |
| 2 | 5 | r.t | 18 |
| 3 | 10 | r.t | 34 |
| 4 | 15 | r.t | 53 |
| 5 | 30 | r.t | 86 |
| 6 | 60 | r.t | 82 |
| 7 | 120 | r.t | 75 |
| 8 | 5 | reflux | 51 |
| 9 | 15 | reflux | 90 |
| 10 | 30 | reflux | 90 |

^a Reaction conditions: **1a** (1 mmol), **2a** (1 mmol), 0.05 g catalyst, MeOH (3 mL), specified temperature for specified time.

^b Isolated yield.

3.5. Study of reusability of the catalyst

To accomplish this study, we examined the reuse of the catalyst. Indeed, a heterogeneous catalyst is not considered interesting in organic synthesis if it can be easily recovered and reused.

After completion of the reaction between 1,2-phenylenediamine and benzaldehyde, the catalyst is recovered by simple filtration and washed with ethyl acetate (2 x 5 mL) to remove all traces of reagents and products final adsorbed on the catalyst, then dried in an oven at 80 °C. The catalyst was reused directly in the model reaction without any additional treatment. The efficiency of the recovered catalyst was measured again by using the same reaction model. As shown in Table 5, the yield of the reaction was reached 67% after 5 cycles suggests with a decrease in its activity after the third use. To the best of our knowledge, the reuse of this catalyst is significantly better than most supported catalysts reported.

TABLE 5
REUSABILITY OF K09 IN THE SYNTHESIS OF BENZIMIDAZOLES BETWEEN **1a** AND **2a**.^a

| Entry | N° of recycling runs | Yield (%) ^b |
|-------|----------------------|------------------------|
| 1 | 1 | 90 |
| 2 | 2 | 89 |
| 3 | 3 | 82 |
| 4 | 4 | 76 |
| 5 | 5 | 67 |

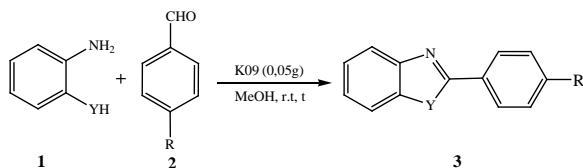
^a Reaction conditions: **1a** (1 mmol), **2a** (1 mmol), catalyst (0.05 g), MeOH (3 ml), reflux for 15 mn.

^b Isolated yield.

3.6. Generalization

Using the optimal conditions, we have extended this study with different aldehydes and o-phenylenediamine for synthesis of various benzimidazoles. The relevant data are presented in Table 6. The yields of the products vary in the range of 82 to 94% depending on the substrate and the conditions used for the reaction (Table 6, entry 1-4).

Under similar condition, the methodology has been extended to the synthesis of various benzothiazoles. The results are summarized in Table 6 (entry 5-8).



Scheme 2 : Generalization of the synthesis of benzimidazoles and benzothiazoles.

TABLE 3
EFFECT OF DIFFERENT SOLVENTS ON THE SYNTHESIS OF 2-PHENYL-1H-BENZIMIDAZOLE CATALYZED BY K09.^a

| Product | Y | R | Temps (min) | Yield (%) ^b |
|-----------|----|-------------------|-------------|------------------------|
| 3a | NH | H | 30 | 86 |
| 3b | NH | 4-Cl | 90 | 94 |
| 3c | NH | 4-NO ₂ | 120 | 85 |
| 3d | NH | 4-Me | 90 | 82 |
| 3e | S | H | 60 | 88 |
| 3f | S | 4-Cl | 75 | 91 |
| 3g | S | 4-NO ₂ | 120 | 84 |
| 3h | S | 4-Me | 90 | 78 |

^a Reaction conditions: benzaldéhyde (1 mmol), 1,2-phénylènediamine (1 mmol), 0.05 g catalyst, solvant (3 mL), r.t. for 60 mn.

^b Isolated yield.

3.7. Comparison of the catalytic activity of K09 and other catalysts

To determine the catalytic activity of K09, we compared the results on the synthesis of benzimidazole with literature data (Table 7). Based on this comparison, it is seen that the catalyst used (K09) has higher returns compared to other reported systems [37-42].

4 GENERAL PROCEDURE FOR THE SYNTHESIS OF BENZIMIDAZOLE DERIVATIVES

In a ballon of 50 ml at round bottom the 1,2-phenylenediamine (1 mmol) and benzaldehyde (1 mmol) were thoroughly mixed in methanol (3 mL). To this mixture the corresponding K09 (0.05g) was added and the resulting mixture was stirred at room temperature for 30 mn (or 15 mn at reflux). After completion of the reaction, the solid resulting was collected by filtration and dissolved in ethyl acetate 10 ml. The catalyst was recovered by simple filtration. After evaporation the solvent, the resulting solid product was recrystallized in ethanol to give the pure product.

TABLE 7
COMPARAISON OF THE CATALYTIC ACTIVITY OF THE K09 IN THE SYNTHESIS OF BENZIMIDAZOLES WITH OTHER REPORTED SYSTEMS.

| Catalyst | Reactions conditions | Times (mn) | Yield (%) | Ref. |
|--|---|------------|-----------|------------|
| K09 | benzaldehyde (1 mmol), 1,2-phenylenediamine (1 mmol), K ₀₉ (0.05 g), R.T, MeOH (3 ml) | 30 | 86 | This study |
| NH ₃ (CH ₂) ₄ NH ₃ SiF ₆ | benzaldehyde (1 mmol), 1,2-phenylenediamine (1 mmol), NH ₃ (CH ₂) ₄ NH ₃ SiF ₆ (1 mol%), solvent free, RT | 4 | 98 | [37] |
| p-TsOH | benzaldehyde (0.5 mmol), 1,2-phenylenediamine (0.5 mmol), p-TsOH (0.1 mmol), 80°C, DMF (2 mL) | 10 | 85 | [38] |
| ceric ammonium nitrate (CAN) | benzaldehyde (1 mmol), 1,2-phenylenediamine (1 mmol), CAN (0.5 mmol), reflux, CH ₂ Cl ₂ (5 mL) | 45 | 75 | [39] |
| (bromodimethyl) sulfonium bromide (Me ₂ S ⁺ BrBr) | benzaldehyde (0.5 mmol), 1,2-phenylenediamine (0.6 mmol), under a nitrogen atmosphere, Me ₂ S ⁺ BrBr (0.5 mmol), R.T, CH ₃ CN (5 mL) | 300 | 85 | [40] |
| CuO-np/SiO ₂ | benzaldehyde (1 mmol), 1, 2-phenylenediamine (1.1 mmol), CuO-np/SiO ₂ (10 mol %), R.T, MeOH (5 ml) | 240 | 93 | [41] |
| Co(OH) ₂ / CoO(II) | benzaldehyde (1.2 mmol), 1,2-phenylenediamine (1.0 mmol), R.T, EtOH | 240/360 | 96/93 | [42] |

✓ SPECTRAL DATA OF TYPICAL COMPOUNDS

2-phenyl-1H-benzo[d]imidazole (3a): m.p.: > 260 °C

¹H NMR (300 MHz, DMSO-d₆) δ_H 12,93 (s, 1H, NH), 7,17-8,18 (m, 9H, ArH) ppm; ¹³C NMR (300 MHz, DMSO-d₆) δ : 151,69; 144,28; 135,47; 130,59; 130,33; 129,43; 126,89; 122,99; 122,19; 119,32; 111,80 ppm

2-(4-nitrophenyl)-1H-benzo[d]imidazole (3b): m.p.: > 260 °C

¹H NMR (300 MHz, DMSO-d₆) δ_H 8,81 (s, 1H, NH), 6,52-8,40 (m, 8H, ArH) ppm; ¹³C NMR (300 MHz, DMSO-d₆) δ : 153,95; 148,80; 145,35; 142,83; 134,38; 129,87; 129,30; 127,87; 124,34; 117,51; 116,48; 115,52 ppm

2-(4-chlorophenyl)-1H-benzo[d]imidazole (3c): m.p.: > 260 °C

¹H NMR (300 MHz, DMSO-d₆) δ_H 12,99 (s, 1H, NH), 6,96-8,18 (m, 8H, ArH) ppm; ¹³C NMR (300 MHz, DMSO-d₆) δ : 150,63; 144,16; 135,46; 134,98; 131,24; 129,53; 129,26; 128,60; 123,26; 122,33; 119,41; 111,90 ppm

2-(p-tolyl)-1H-benzo[d]imidazole (3d): m.p.: > 260 °C

¹H NMR (300 MHz, DMSO-d₆) δ_H 12,80 (s, 1H, NH), 7,15-8,19 (m, 8H, ArH), 2,35 (s, 3H, CH₃) ppm; ¹³C NMR (300 MHz, DMSO-d₆) δ : 151,85; 144,20; 140,05; 129,98; 128,85; 127,87; 126,85; 122,81; 122,04; 119,15; 111,63; 21,42 ppm

2-phenylbenzothiazole (3e): m.p.: 110-114 °C

¹H NMR (300 MHz, DMSO-d₆) δ_H 7,41-8,08 (m, 9H, ArH) ppm; ¹³C NMR (300 MHz, DMSO-d₆) δ : 167,77; 154,02; 134,92; 133,31; 131,87; 129,86; 127,65; 127,13; 126,01; 123,35; 122,80 ppm

2-(4-nitrophenyl)benzothiazole (3f): m.p.: 226-228 °C

¹H NMR (300 MHz, DMSO-d₆) δ_H 6,51-8,21 (m, 8H, ArH) ppm; ¹³C NMR (300 MHz, DMSO-d₆) δ : 159,44; 149,69; 148,35; 141,72; 132,21; 130,32; 128,84; 127,59; 126,77; 124,92; 123,95; 122,97; 119,77; 67,79 ppm

2-(4-chlorophenyl)benzothiazole (3g): m.p.: 114-116 °C

¹H NMR (300 MHz, DMSO-d₆) δ_H 7,29-8,11 (m, 8H, ArH) ppm; ¹³C NMR (300 MHz, DMSO-d₆) δ : 166,45; 153,92; 139,23; 136,49; 132,12; 129,93; 128,71; 127,27; 126,22; 123,43; 122,89 ppm

2-(p-tolyl)benzothiazole (3h): m.p.: 86-88 °C

¹H NMR (300 MHz, DMSO-d₆) δ_H 7,29-8,06 (m, 8H, ArH), 2,33 (s, 3H, CH₃) ppm; ¹³C NMR (300 MHz, DMSO-d₆) δ : 167,82; 154,05; 141,90; 134,78; 130,70; 130,33; 127,55; 127,01; 125,79; 123,15; 122,66; 21,45 ppm

5 CONCLUSION

In summary, benzimidazoles and its derivatives have been synthesized by the coupling of the 1,2-phenylenediamine with aldehydes using K09 as efficient recyclable catalyst in methanol at room temperature. Benzimidazoles could be successfully synthesized by using this catalyst. The reactions were performed in methanol and catalyst can be reused for several cycles without much decrease in its activity. The main features of this process include mild conditions, short reaction time, high yields, recyclable catalyst, large scale synthesis, and simple procedure. This catalyst can replace the existing heterogeneous and homogeneous catalysts expensive, which are currently used in the synthesis of various industrially important benzimidazoles and biologically active.

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