A Mild and Efficient one-pot Synthesis of 2-substituted Benzimidazoles through a New Surfactant-modified Moroccan Clay Catalyst

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A simple and convenient synthesis of 2-substituted benzimidazoles, using o-phenyldiamine as starting material with several aldehydes, has been accomplished by heterogeneous catalysis using a small amount of a new surfactant-modified Moroccan Ghassoulite clay catalyst. The reaction was carried out under very mild conditions at room temperature. The catalyst can be easily regenerated and reused. The yields obtained are very good in reasonably short time.

Keywords: Moroccan Ghassoulite Clay, catalyst, O-phenyldiamine, benzimidazoles

Benzimidazoles, which are analogues of imidazole contained in histidine, are an important pharmacophore and privileged structural core in medicinal chemistry [1] (fig. 1). Several compounds containing the benzimidazole scaffold have been used as antitumoral [2], antimicrobial [3], antihistaminic [4], antiparasitic [5], antifungal [6], vasorelaxant agents [7], and against several viruses such as HIV [8], RNA [9], and influenza [10]. Therefore, the preparation of benzimidazoles has gained considerable attention in recent years [11].

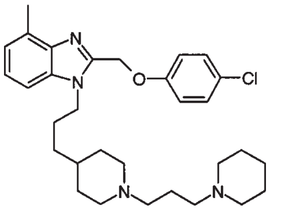


Fig. 1. NPY1 Receptor Antagonist

Usually, methods of benzimidazole synthesis include the cyclocondensation of aryldiamines either with the corresponding carboxylic acids under harsh dehydrating reaction conditions [12] or with aldehydes under oxidative conditions [13]. The condensation of *o*-phenylenediamines and the aldehydes requires an oxidative reagent to generate the benzimidazole core. Various reagents such as nitrobenzene [14], sodium metabisulfite [15], benzoquinone [16], In(OTf)$_3$ [17], I$_2$/KI [18] and even air [19] have been employed for this purpose. Recently, have been synthesised the benzimidazoles using trichloroisocyanuric acid as the oxidant [20].

Unfortunately, many of these processes suffer some limitations, such as low yields, long reaction times, drastic reaction conditions, tedious work-up procedures, and co-occurrence of several side reactions. Moreover, the main disadvantage of almost all existing methods is that the catalysts are destroyed in the work-up procedure and cannot be recovered or reused. Consequently, it is desirable to develop an easy manipulative procedure, as well as to avoid strong acids and other corrosive media and replacing hazardous or expensive reactants and reagents by safer, environmentally friendly, non-toxic, recoverable, reusable, economical ones.

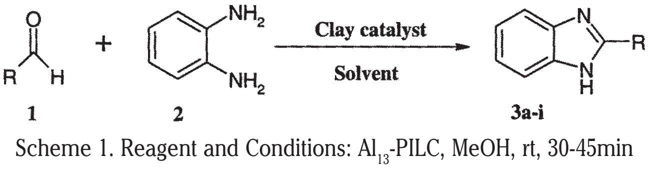
An important family of catalyst that received considerable attention in recent time is derived from the soil. The most noteworthy ones being zeolites and clays in particularly pillared interlayered clays (PILCs) [21].

The applications of inorganic solids such as pillared clays (PILCs) as efficient catalysts of inorganic transformations have been exploited recently for several reactions [21], due to their larger pores than traditional zeolites.

Pillared interlayered clays (PILCs) or pillared clays constitute one of the most studied families of the new microporous materials developed by molecular engineering. These solids are prepared by a multi-step synthesis process, which mainly involves the exchange of the charge balancing cations of smectitic clays by bulky inorganic polyoxocations, and the stabilization of the intercalated solids thus generated by calcination. Aluminum-pillared clays are the most documented pillared clays, mainly because the synthesis of the intercalating polycation $[Al_{13}(O)_4(OH)_{24}(H_2O)_{12}]^{7+}$ usually known as Al$_{13}$ [22], is a simple and reproducible. But other cations can be used in the pillaring of clay minerals [23]. The Al$_{13}$-PILC material used in the present study was prepared with a purified Moroccan clay mineral from Moulouya known as a Ghassoulite or Rhassoulite [24].

Rhassoule is mined only in the Atlas Mountains of Morocco, and has been used for centuries throughout the Middle East as a skin and hair cleanser.

The work described in this paper was carried out to expand the scope of this modified natural Moroccan Ghassoulite clay, not yet exploited in the organic synthesis, by applying it to the synthesis of benzimidazole (scheme 1, table 1).



Scheme 1. Reagent and Conditions: Al$_{13}$-PILC, MeOH, rt, 30-45min

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	SiO_2	Al_2O_3	MgO	MnO	Li_2O	K_2O	CaO	Na_2O	Fe_2O_3	SO_3	Total
ghassoulite	64.57	2.06	23.63	0.41	0.28	2.84	1.84	1.52	0.84	1.91	99.90
Al_{13}-PILC	64.49	9.34	22.82	0.40	0.26	0.03	0.00	0.65	0.81	1.12	99.97

Table 1
CHEMICAL COMPOSITION OF THE SAMPLES STUDIED (METAL OXIDES IN wt.%)

	BET ads.N_2 at 77k	BJH ads.N_2 at 77k	BJH ads. Cumulative pore volume[a]	
	S_{BET} ($m^2.g^{-1}$)	V_μ ($cm^3.g^{-1}$)	V_p ($cm^3.g^{-1}$)	d_{001} (Å)
Na-Gh	414	0.0045	0.72	12.4
Al_{13}-PILC	571	0.039	0.61	18.2

[a] *Pores between 1.7 and 300 nm diameter.*

Table 2
CHARACTERISTICS OF Na-Gh AND MODIFIED SAMPLE AL-PILC

Results and discussion

The pillaring oligocation was prepared from 0.2 M of AlC_{13}, $6H_2O$ solution and 0.2 M of NaOH solution with a basicity ratio of OH/Al = 2.2. The Na-exchanged ghassoulite [24] was re-dispersed in a solution made of 2.5% clay in demineralised water and stirred for 24 h. The polymeric solution was incorporated drop by drop into the Na-exchanged slurry. The amount of the incorporated oligocation had a ratio of 10 mmol of Alg^{-1} of clay. The *p*H of this mixture was adjusted to 3.8 and the mixture was stirred for at least 12 h. The resulting material was centrifuged and washed until no chloride was present in the wash water. The resulting solid was then dried overnight at 100°C in a conventional draying oven, and then calcined at a heating rate of 2°C/min to 450°C and kept at this temperature for 4 h. The resulting material was denominated Al_{13}-PILC. The final product is identified by X-ray diffraction with a Siemens D-5000 Diffractometer (Cu-K_radiation, λ= 1.5405 Å), the surface area were obtained from the BET [25] treatment of the isotherms in the range of relative pressures 0.05–0.25, while the BJH [26] method was used to determine the pore surface areas, the pore volumes and the micropore volumes (tables 1 and 2) [24].

The catalytic activity of the new material in the synthesis of benzimidazoles was assessed at room temperature and atmospheric pressure using *o*-phenylenediamine as starting material with several aldehydes.

General reaction procedure for the synthesis of benzimidazoles from aldehydes and diamines are described in table 2: To a flask containing a mixture of *o*-phenylenedianmine **1** (1 mmol) and benzaldehyde **2** (1.1 mmol) in methanol (3 mL), clay catalyst (0.1 g) was added and the mixture was stirred at room temperature until completion of the reaction, as monitored by thin layer chromatography (TLC). The reaction mixture was filtered and the catalyst washed with methanol. After concentration of the filtrate under reduced pressure, the residue was purified by silica gel column chromatography (ethyl acetate/hexane: 2:3) to afford the desired product **3** (table 3). The analytical data were identical with those reported by the literature.

2-(4-Methoxyphenyl)benzimidazole **3e**: ^{1}H NMR ($CDC1_3$): δ 3.84 (s, 3H) 7.24 (d, *J* = 8.8 Hz, 2H), 7.48 (m, 2H), 7.74 (m, 2H), 8.08 (d, *J* = 8.8 Hz, 2H). MS: m/z 225 [M+1]. 2-(4-Methylphenyl)benzimidazole **3g**: ^{1}H NMR (DMSO-d_6): δ 2.36 (s, 3H), 7.20 (m, 2H), 7.25 (d, *J* = 8.0 Hz, 2H), 7.64 (m, 2H), 8.15 (d, *J* = 8.0 Hz, 2H), 12.45 (br s, 1H). MS: m/z 209 [M+1].

As shown in table 3, aromatic, aliphatic, and unsaturated aldehydes react without any significant difference in rates to give the corresponding 2-substituted benzimidazoles in

Entry	R	Product	Reaction time (min)	Yields (%)	Physical state mp(°C)(mp litt.)
1	C_6H_5	**3a**	30	95	285.5 (286-289)[17]
2	3-NO_2-C_6H_4	**3b**	25	90	206 (204-206)[29]
3	4-NO_2-C_6H_4	**3c**	45	84	298 (297-299)[29]
4	4-Cl-C_6H_4	**3d**	45	80	301.5 (301–303)[17]
5	4-MeO-C_6H_4	**3e**	30	98	226 (226-227)[30]
6	4-HO-C_6H_4	**3f**	35	93	255 (254-256)[7]
7	4-Me-C_6H_4	**3g**	45	90	275 (275-276)[30]
8	C_5H_{11}	**3h**	45	80	164.5 (164–165)[17]
9	CH═CH–C_6H_5 (*E*)	**3i**	45	85	202 (201–203)[17]

Table 3
Al_{13}-PILC –CATALYZED FORMATION OF BENZIMIDAZOLES

Table 4
EFFECT OF SOLVENT ON THE ACTIVITY OF THE CATALYST
IN THE SYNTHESIS OF **3a** AFTER 30 mn

Solvent	Yield (%)
Hexane	30
Ethanol	77
Chloroform	40
Methanol	95
Acetone	23
DMF	0

good to excellent yield and in reasonably short time. Condensation of related *o*-phenylenediamine with appropriate benzaldehyde was already achieved without any catalyst using drastic conditions [27]. In our study, we prove that the addition of catalyst with mild conditions smoothly oxidized the condensed products of aldehydes and o-phenylenediamine to benzimidazoles.

In the presence of Al_{13}-PILC various solvents were tested. Thus, after 30 min of reaction the yields obtained of product **3a** are shown in the table 4.

The solvents protic (alcohols) proved all good for the condensation of diamines and aldehydes aromatic. However the catalytic effectiveness of our support decreases with the size of solvent: Methanol (95%) > Ethanol (77%) > Chloroform (40%) > Hexane (30%)> Acetone (23%). This sequence is conceivable if one refers to the possibility of adsorption of hydrogen of the grouping OH in the pores of catalyst to intervene thereafter the activation of the reagents. In the cases of dimethylformamide no product **3a** was observed under the reaction conditions, only the starting material was isolated.

A solid catalyst is especially interesting when we can use it several times. This reuse gives the catalyst an advantage compared to other catalysts. Thus, the used and recovered Al_{13}-PILC has been shown to be reusable, after washing/centrifugation with methanol (two times), with acetonitrile (one time) and drying at 150°C in vacuum, without appreciable loss of activity.

Conclusion

In summary, we have reported an efficient and convenient route to the heterogeneous synthesis of several benzimidazoles substituted in position 2 using modified Moroccan clay. This new catalyst can be easily regenerated. The yields obtained are very good in reasonably short time.

The further application of this new catalyst for the synthesis of other heterocycles will be described in due course.

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