Catal Lett (2009) 129:281–286
DOI 10.1007/s10562-008-9817-6

Microwave Assisted *Green* Synthesis of Long-chain 1-Alkylimidazoles and Medium-chain 1-alkyl-2-Methylimidazoles with Antiviral Properties Catalyzed by Basic Carbons

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Received: 11 November 2008 / Accepted: 4 December 2008 / Published online: 23 December 2008

Abstract Long-chain 1-alkylimidazoles and medium-chain 1-alkyl-2-methylimidazoles have been prepared by conventional thermal activation, in a batch reactor system, and microwave activation using alkaline promoted carbons, Na-Norit, Cs-Norit and NaCs-Norit in absence of any solvent. Till now some authors had reported the synthesis of medium-chain 1-alkylimidazoles with antiviral properties using other basic media. Under the experimental conditions, 1-nonylimidazole, 1-dodecylimidazole, 1-butyl-2-methylimidazole and 1-hexyl-2-methylimidazole can be prepared with a high conversion and selectivity. The physicochemical characterization of the carbon catalysts was carried out by thermal analysis, nitrogen adsorption, X-ray photoelectron spectroscopy and Knoevenagel condensation as a probe reaction. Most of the basic sites in the promoted carbons have strength in the range $9 \leq \mathrm{p}K_\mathrm{a} \leq 16.5$ that convert them in appropriate catalysts able to abstract the proton of imidazolic rings to be attacked by alkylhalides.

Keywords Long-chain 1-alkylimidazoles and medium-chain 1-alkyl-2-methylimidazoles · Basic carbons · Microwave irradiation · Green chemistry

1 Introduction

Industrial chemistry in the new millennium is widely adopting the concept of "green chemistry" to meet the fundamental scientific challenges of protecting human health and the environment while simultaneously achieving commercial profitability [1]. One of the approaches for achieving this target is to explore alternative reaction conditions and reaction media to accomplish the desired chemical transformations with minimal by-products, as well as eliminating the use of conventional organic solvents, if possible. Some of the important alternative tools include the use of microwaves (MW) as alternative source. Chemical reactions are accelerated because of selective absorption of MW energy by polar molecules. The short reaction time, and expanded reaction range that is offered by MW assisted synthesis are suited to the increased demands in industry, in particular, in the pharmaceutical industry [2, 3].

Activated carbons have been used to catalyze efficiently organic synthesis, because of their extended surface area, microporous structure, and high degree of surface reactivity [2]. Carbon is known in microwave terminology as a very "lossy" material, a very efficient absorber of MW energy and converts that energy to heat. Martín-Aranda and coworkers [3] have reported that alkaline carbons are appropriate solids to catalyze selectively base reactions and in particular the imidazole *N*-alkylation with 1-bromobutane under microwave activation. The 1-alkylimidazoles of type A (Scheme 1) exhibit a variety of valuable pharmacological properties (antiparasitic, antifungal and antimicrobial activity) and in the literature has been reported that the length of the alkyl chain on the imidazole ring and the presence of the substituting ligands in the imidazole ring, play an important role in the biological activity showed by the final 1-alkylated imidazole product [4].

In this context, we have extended our researches and report the conventional thermal and the microwave assisted *N*-alkylation of imidazole and substituted 2-methylimidazole

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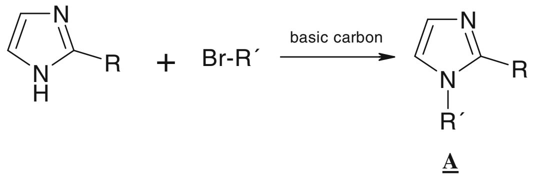

Product (A)	R	R´
1-alkylimidazole	H	C_9H_{18}, $C_{10}H_{30}$, $C_{12}H_{24}$
1-alkyl-2-methylimidazole	CH_3	C_4H_8, C_6H_{12}

Scheme 1 *N*-alkylation of imidazole and 2-methylimidazole with long-chain and medium-chain akylhalides

with long-chain and medium-chain alkylbromides, respectively to obtain 1-nonylimidazole, 1-dodecylimidazole, 1-butyl-2-methylimidazole and 1-hexyl-2-methylimidazole (Scheme 1).

2 Experimental

2.1 Catalysts Preparation and Characterization

The pristine activated carbon RX-1.5-EXTRA Norit was treated with the corresponding aqueous alkaline chloride solution (2 M) at 358 K for 70 h, using a liquid/solid ratio of 10. The samples were filtered and washed with distilled water until chloride free. After drying at 383 K for 48 h the resulting carbons were pelletized, crushed and sieved to particle size $\phi < 0.140$ mm diameter.

The alkali-loaded catalysts Na-Norit, Cs-Norit and the bimetallic NaCs-Norit were characterized following different physicochemical techniques. The ash contents of the catalysts were obtained by thermogravimetric analysis (TG/DTA Seiko System 320). The pH of the samples were measured following the method described by Rivera et al. [5] using an Omega pH-meter, model PHB-62 (Table 1).

Specific surface areas of the carbon samples were determined by N_2 adsorption isotherms at 77 K, applying the BET method [6] in a Micromeritics ASAP 2010 Volumetric System. Volume adsorbed in the different types of pores was calculated by the DFT (Density Functional Theory) method [7] by means of DFT plus software. Table 2 shows the specific surface areas and the adsorbed volume obtained for the carbon catalysts. Table 2 also shows the values of the microporous area and the volume of the micropores obtained by CO_2 adsorption at 273 K using the Dubinin–Radushkevich (DR) equation and the DFT method.

Table 1 Specific area, pH, and metal contents of the catalysts

Catalyst	pH	Ash (%)	M_2O (%)	Metal (at g/100 g cat.)
Norit	7.05	4.3	–	–
Na–N	7.17	5.1	0.8	0.013
Cs–N	7.58	5.2	0.9	0.003
NaCs–N	7.51	5.4	1.1	–

Table 2 Textural characterization of the samples

Catalyst	S_{BET} (m^2/g)	V_{tot} (cm^3/g)	$S_{micropore(D–R)}$ (m^2/g)[a]	$V_{micropore(D–R)}$ (cm^3/g)[a]
Norit	1450	0.571	554	0.201
Na–N	1375	0.570	300	0.109
Cs–N	1447	0.543	370	0.135
NaCs–N	1338	0.555	460	0.167

(Micropore: $\phi < 2$ nm; mesopore $2 < \phi < 50$ nm. V_{tot}: volume adsorbed by the pores $\phi < 200$ nm)

[a] Calculations were carried out using the Dubinin–Radushkevich (D–R) equation with the data obtained from CO_2 adsorption

The X-ray photoelectron spectroscopy (XPS) technique was employed to find out the chemical state and the relative dispersion of the alkali metals deposited on the surface of the carbon of the samples. Photoelectron spectra (XPS) were acquired with a VG ESCALAB 200R spectrometer equipped with a hemispherical electron analyzer and MgKα ($h\nu = 1{,}253.6$ eV, 1 eV $= 1.6302 \times 10^{-19}$ J) X-ray source. The powder samples were pressed into aluminum holders and mounted on a sample rod placed in the pretreatment chamber of the spectrometer. After outgassing 1 h at room temperature, they were placed into the analysis chamber. The residual pressure in the ion-pumped analysis chamber was maintained below 5×10^{-9} Torr during data acquisition. The intensities of C1s, O 1s, and Na1s or Cs $3d_{5/2}$ peaks were estimated by calculating the integral of each peak after smoothing and subtraction of the "*S*"-shaped background and fitting the experimental curve to a combination of Gaussian and Lorentzian lines of variable proportion. The binding energies (BE) were reference to the major C 1s component at 284.9 eV, this reference giving BE values with an accuracy of ±0.1 eV.

The chemical characterization of the active sites present in the activated carbon-supported catalysts Na-Norit, Cs-Norit and NaCs-Norit was carried out using the basicity probe reaction of Knoevenagel condensation between benzaldehyde and malonic esters of different pK_a (ethyl cyanoacetate, $pK_a = 9$; ethyl acetoacetate, $pK_a = 10.7$; diethyl malonate, $pK_a = 13.3$ and ethyl bromoacetate, $pK_a = 16.5$) as a catalytic basicity-Test reaction. An equimolar solution (9 mmol) of the two reactants without any solvent was kept in a batch reactor in a silicone bath under magnetic stirring, while heating up to the reaction temperature (363–433 K). Then, 1, 2, 10 and 12 wt% of catalyst was added and the reaction time started. Samples were taken periodically and the evolution of the reaction between 1 and 4 h was followed by GC–MS, Agilent 6890 GC and mass spectrometry, Hewlett–Packard HP 5971 A [7].

2.2 Activation and Reaction Procedures

2.2.1 *Thermal Induced Reactions*

Mixture of imidazole (1.5 mmol) and alkylhalides (7 mmol) was heated in a batch reactor and in absence of any solvent at 313, 333 and 353 K, respectively, under vigorous stirring. Then, the catalyst was added and the reaction time started. After cooling, the reaction products were extracted with acetone (20 mL) and filtered. The reactions were followed by gas chromatography, Agilent 6890 GC and mass spectrometry, Hewlett–Packard HP 5971 A. The reactivity is expressed in terms of the amount of A obtained in wt%.

2.2.2 *Microwaves Induced Reactions*

Activity and selectivity of the catalysts under microwave activation, were determined using a multimode microwave oven. A sealed microwave PTFE Teflon vessel was used. The microwave equipment employed in this work is a SAMSUNG M-1827-N multimode microwave oven operated at the fixed-frequency of 2,450 MHz.

Imidazole (1.5 mmol) and 0.02 g of the catalyst were blended in the Teflon vessel and alkyl bromide (7.1 mmol) was added. The mixture was irradiated in the microwave at different powers (100–300 W) and different times of reaction 1–3 min. After cooling, the reaction products were extracted with acetone (20 mL) and filtered. The isolated catalyst was then washed with distillate water and dried at 150 °C for 2 h to be reused in a new cycle of reaction. The reaction was followed as described above.

3 Results and Discussion

3.1 Characterization Results

The alkali-doped activated carbons (Na-Norit, Cs-Norit and NaCs-Norit) were physically and chemically characterized showing basic properties.

Table 1 summarizes the apparent specific area, the pH and the metal contents of the catalysts. The pristine carbon, RX-1 EXTRA Norit, exhibits a pH of 7.05, which increases only slightly in the sample exchanged with sodium or/and cesium, respectively in the range 7.17–7.51.

The ash contents of the studied catalysts obtained by thermogravimetric analysis (Table 1) showed that the exchange capacity of Norit RX-1.5 EXTRA carbon for sodium (ionic radius = 0.095 nm) is around four times the exchange capacity for cesium (ionic radius = 0.169 nm) due to the higher diffusional barrier that the Cs^+ ions has to overcame to access the interior of the micropores of the carbon support.

In order to get a more precise idea about the chemical state and the relative dispersion of the alkaline metals at the surface of the carbon, a surface analysis of the different samples by X-ray photoelectron spectroscopy was carried out. The BEs of C 1s and O 1s core levels and the characteristic inner levels of the alkaline elements are given in Table 3, together with the M/C atomic ratios, determined from the peak intensities and the tabulated sensitivity atomic factors [8]. In general, in all the samples, the C1s core level presented three peaks, one of them, at 284.5 eV was due to the >C=C< bonds of the carbon structure or to the non-functionalized –CH– species which still conserved hydrogen atoms. Although they present a small chemical shift with respect to the peaks due to the >C=C< bonds, this shift is so small that the instrument cannot distinguish it. The second peak appears approximately at 285.9 eV showing approximately a 25–39% contribution to the total area and is assigned to C–O species, and the third peak at 288.0 eV, with lower intensity corresponds to the functional groups that contain >C=O species.

The values of the bond energies of core level O1s gave information of the nature of the oxygenated surface groups that were present on the carbon surface of the samples. In the O1s level there were two peaks, one of them, near 531 eV, was due to species of type C=O (carboxyl and lactone groups) of the carbon support; the other peak, near 533 eV, is due to species of type $C–O^-$ (phenol or ether group) belonging to the structure of the carbon and possible oxide species formed when the alkali or alkaline earth species interacted with the surface oxygenated groups present in the structure of the carbon. In Table 3 it can be observed that the percentage corresponding to this peak grew with respect to the peak of the pristine Norit carbon for the alkali-Norit samples, confirming the formation of oxide type species in the treated carbons. In addition, the binding energies of the internal electrons of the alkali/alkaline earth atoms adjusted to oxide type species although the binding energies of the carbonate type species are very similar and therefore the presence of a small proportion of these types of species could not be discarded. These carbonate type species would be originated by the formation of alkali metal-oxygen groups which would have been formed when the metallic cations react with the surface oxygenated species of the surface of the carbon which would next have been oxidized during the manipulation of

Table 3 Binding energies (eV) of the internal electrons and surface atomic relations of the basic alkali-Norit carbons

Catalyst	C 1s	O 1s	M1s (2p, 3d)	O_{total}/C_{total} at	Atomic relation M/C	
					Ba(Cs)/C	Mg/C at
C(Norit)	284.5 (65)		–	0.040		
	285.9 (25)	531.8 (59)				
	288.0 (10)	533.5 (41)				
Na–C(Norit)[a]	284.5 (62)		–	0.075		
	285.9 (27)	531.8 (51)				
	288.0 (11)	533.5 (49)				
Cs–C(Norit)	284.5 (62)		727.4	0.093	0.004	
	285.9 (27)	531.7 (49)				
	288.0 (11)	533.5 (51)				
NaCs–C(Norit)[a]	284.5 (63)		727.5	0.080	0.005	
	285.9 (27)	531.8 (45)				
	288.0 (10)	533.5 (55)				

The values in parentheses indicate the % of each peak

[a] No sodium was detected

the samples. Table 3 also shows the O_{total}/C_{total} relation, which indicated the degree of oxidation of the surface of the samples. When observing these values, it is seen that the content in oxygen increased in the treated carbons, which confirmed the formation of new oxygenated groups on the surface of the samples, oxygenated surface groups of the carbon structure and alkali/alkaline earth oxide and/or carbonate species.

In addition, the concentration of the alkali elements that were incorporated in the activated Norit carbon used to prepare the alkali-Norit samples was calculated. In order to do so, the intensities of the peaks, corrected by the atomic sensitivity factors, were measured. Table 3 shows that the M/C relation was not high (0.003–0.012). During the adsorption-impregnation process, the M^+ cations (catalysts Na-Norit and NaCs-Norit, Na^+; Cs-Norit and NaCs-Norit, Cs^+) would interact by electrostatic forces with the surface groups present on the surface of the carbon. However, when accessing the sites located in the micropore of the substrate and due to steric hindrance, two important variables had to be taken into account: ionic radius and the charge of the cation (polarization capacity charge/radius). As the charge/cation radius increases, the diffusion barrier, which has to be overcome to access the interior of the micropore, is higher, and therefore they tend to stay on the surface. For the Na-Norit sample, it was not possible to detect Na^+ on the surface of the carbon by this study since its low charge/radius relation allowed it to access the interior of the porous structure of the carbon and its small radius allowed it to enter the micropores. In the case of the Cs-Norit sample, although it has a lower charge/radius relation than Na^+, it was possible to detect the presence of Cs on the surface since this cation found a greater difficulty in accessing the micropores due to its higher radius. These data were contrasted with the ones obtained by thermal analysis and surface area measurements.

Using the Knoevenagel condensation as a basicity probe reaction for inorganic solids, it has been found that most of the active sites in the alkaline promoted carbons have $9 \leq pK_a \leq 16.5$. Considering that the NH group of imidazole presents a $pK_a = 14.5$ [9] and in case of 2-methylimidazole presents a $pK_a = 7.8$ [10] these carbons are appropriate catalysts to abstract the proton of the NH group and to perform the imidazole alkylation.

3.2 Activated Reactions Under Conventional Thermal Activation and Microwave Activation

The *N*-alkylation of 2-methylimidazole with 1-bromobutane and 1-bromohexane and the *N*-alkylation of imidazole with 1-bromononane, 1-bromododecane and 1-bromododecane was performed on the basic carbons catalysts under conventional thermal activation and under microwave activation, in absence of any solvent. Under our experimental conditions, 1-substituted imidazoles and 1-substituted 2-methylimidazoles of type A were selectively obtained and no other products were formed.

The microwave irradiation in combination with alkaline carbons provides very short times and very mild conditions of reactions an interesting reactivity and selectivity, being an environmentally friendly process [3, 11–14].

Figure 1 shows the results obtained under conventional thermal activation for the alkali catalyst NaCs-Norit. The order of reactivity found for the employed alkyl halides was the following one: 1-bromononane > 1-bromodecane > 1-bromododecane, there being reached in all the cases

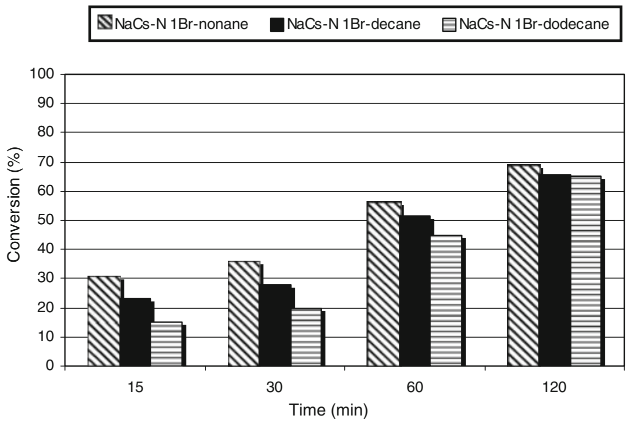

Fig. 1 *N*-alkylation of imidazole (1.5 mmol) and alkyl halides of long-chain (7.1 mmol) under conventional thermal activation (batch) at 333 K using NaCs-Norit as catalyst (0.02 g)

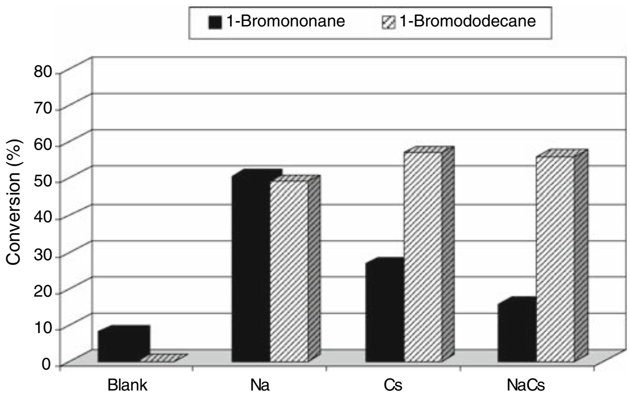

Fig. 2 Microwave activated *N*-alkylation of imidazole (1.5 mmol) with long-chain alkylbromides (7.1 mmol); $t = 3$ min, $P = 100$ W and 0.02 g of catalyst

conversions superior to 60% for 120 min of reaction. The reactivity of the alkyl halides diminish with the length of the chain decreasing the conversion of the reaction till 60 min, from this moment conversions were almost equal at 120 min of reaction for all the employed alkylhalides.

Figure 2 shows the conversion obtained using imidazole and long-chain alkyl bromides under microwave activation. In the case of imidazole *N*-alkylation with the longest chain alkyl bromide (1-bromododecane), yields of 50% were obtained when Cs-Norit and NaCs-Norit catalysts were employed in only 3 min at 100 W of irradiation power. In the case of Na-Norit catalyst the reached conversion was slightly inferior getting almost the same value when 1-bromononane was used as alkyl halide while lower conversions were reached for Cs-Norit and NaCs-Norit.

The results obtained when 2-methylimidazole and medium-chain alkyl halides where employed again demonstrate that microwave activation performs much better

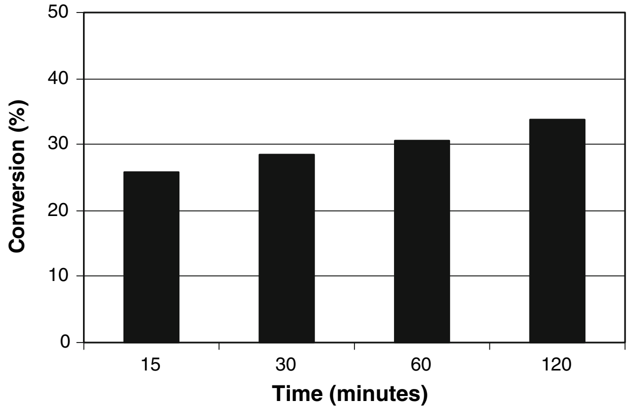

Fig. 3 *N*-alkylation of 2-methylimidazole (1.5 mmol) with 1-bromohexane (7.1 mmol) under convectional thermal activation (batch) at 313 K using NaCs-Norit as catalyst (0.02 g)

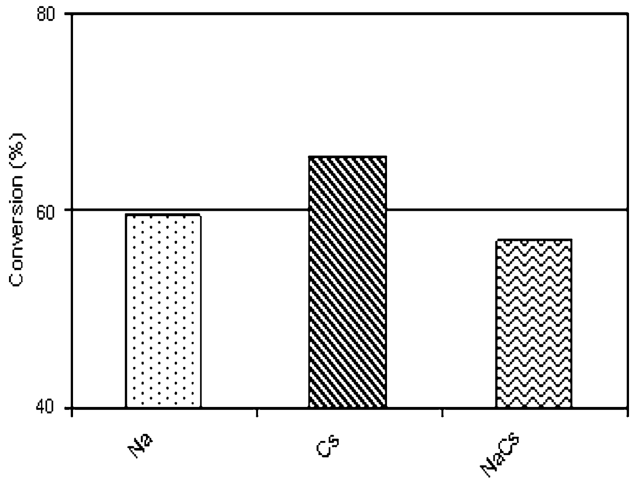

Fig. 4 Microwave activated *N*-alkylation of 2-methylimidazole (1.5 mmol) with medium-chain alkylbromides (7.1 mmol) (1-bromobutane); $t = 3$ min, $P = 300$ W and 0.02 g of catalyst

than thermal activation since Cs-Norit affords conversions higher than 60% and selectivity's of 100% in the production of 1-butyl-2-methylimidazole at 3 min and 300 W of power as shows Fig. 3. In the production of 1-hexyl-2-methylimidazole, 33.7% of conversion was achieved at 313 K in 2 h over NaCs-Norit catalyst as it can be observed in Fig. 4 whereas conversions of ~20% are achieved in only 1 min and 300 W of irradiation power. The used of substituted imidazoles and long-chain alkyl agent decreased the final values of conversion due to the major steric impediment but increase the antiviral activity of the final product. In any case our basic carbons under microwave activation turned out suitable catalysts to carry out the proposed reaction in very short times and under mild conditions being also able to be reused in four cycles of reaction without important changes in the final yield of the reaction.

4 Conclusions

Alkali carbons were found to be very efficient catalysts for the *N*-alkylation of imidazolic heterocycles under conventional thermal and microwave activation. The basicity of the carbon is enhanced by the presence of the alkali metal on the surface. The microwave heating can greatly improve the conversion and selectivity of *N*-alkylation of the heterocycle over alkali promoted carbons. Under these experimental conditions, the formation of environmental hazardous residues is avoided. It can be concluded that the conversion of imidazole increases for microwave activated reactions, being reached 50% of conversion in case of *N*-alkylation of imidazole with long-chain alkyl halides in 3 min when only 100 W of power is applied and 3 min are used. Conversion values of 60% with 100% of selectivity are obtained in only 3 min of reaction and 300 W of microwave power when 2-methylimidazole is alkylated with medium-chain alkyl halides. These results show the great usefulness of the microwave irradiation of a basic carbon catalyst in the target reaction. This environmentally friendly process can be extended to the preparation of other 1-long chain unsubstituted heterocycles and medium-chain substituted heterocycles with improved pharmaceutical properties that are key precursors for many fine chemicals.

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