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Alkaline carbons as effective catalysts for the microwave-assisted synthesis of N-substituted-gamma-lactams

V. Calvino-Casilda[a,*], R.M. Martín-Aranda[b], A.J. López-Peinado[b]

[a] *Catalytic Spectroscopy Laboratory, Instituto de Catálisis y Petroleoquímica (CSIC), Marie Curie 2 E-28049 Madrid, Spain*
[b] *Dpto. Química Inorgánica y Química Técnica. Universidad Nacional de Educación a distancia (UNED), Senda Del Rey 9 E-28040 Madrid, Spain*

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ABSTRACT

The selective construction of new C—C or C—heteroatom bonds is frequently the fundamental step in the synthesis of derivatives with high added value. In particular, molecules with C—N bonds are of great interest due to their widespread use and intrinsic importance. Of the large number of organic compounds with useful biological activity, organic compounds with C—N bonds are among the most prominent. For instance, the nitrogenated gamma-lactamic heterocycles are the basic structures of many substances used as intermediates in the synthesis of important compounds with pharmacological properties such as psychotropics and antihypertensives as well as others with biological properties. In the present work, we reported for the first time an efficient and eco-friendly alternative to obtain N-substituted-gamma-lactams by carbon–nitrogen coupling of 2-pyrrolidinone and 1-heptanal assisted by microwave irradiation, over activated alkali-Norit carbon catalysts in solvent-free conditions.

1. Introduction

The synthesis of derivatives with high added value (Fine Chemicals) as well as the production of commodity and special polymers requires a fundamental step based mainly on the selective construction of new C—C or C—heteroatom bonds. In particular, among the large number of organic compounds with useful biological activity, organic compounds with C—N bonds are one of the most prominent. For instance, the construction of C—N bonds by N-subtititution of nitrogenated heterocycles as gamma-lactams, is of great interest since they are the basic structures of many intermediates used in the synthesis of compounds with important biological properties as kaitocephalin, lemonomycin and aeuroginosin [1–3] and others with pharmacological properties related to the area of neuroexcitatory chemistry [4] as psychotropics, antihypertensives and compounds with antimuscarinic activity [5–10]. The functionalized gamma-lactams including functionalized pyrrolidinones not only have antibacterial properties but have also recently been used as promoters of conformation control of peptides [11–14] as well as intermediates for the synthesis of agrochemicals, textile auxiliaries, solvents, polymers, stabilizers, dyes and nylon precursors [15,16].

One of the approaches for achieving the fundamental scientific challenges of green chemistry 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 [17]. Some of these important alternative tools include the use of microwave irradiation. Microwave-assisted 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 [18–21].

The objective of this contribution is to demonstrate that the carbon–nitrogen (hetero) coupling reaction between gamma-lactams (2-pyrrolidinone) and aldehydes (1-heptanal) (Scheme 1) can be carried out successfully combining carbon catalysts and microwave activation in absence of any solvent. Under mild conditions, the authors have developed a remarkable fast one-pot synthesis of N-substituted-gamma-lactams. Kinetics and mechanism of the reaction as well as the influence of external reaction parameters such as basicity (alkaline promoter supported on the carbon) have been also investigated comparing the results obtained under microwave activation with those obtained under conventional thermal activation.

In the literature is described that N-α-hydroxialkylated-lactams of type A (Scheme 1) are the main reaction product obtained in the carbon–nitrogen (hetero) coupling reaction over basic catalysts under conventional thermal activation [10]. In the present

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* Corresponding author. Tel.: +34 915854879.
E-mail address: vcalvino@icp.csic.es (V. Calvino-Casilda).

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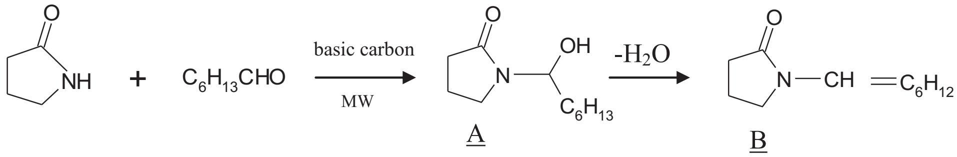

Scheme 1. N-substitution of 2-pyrrolidinone with 1-heptanal under microwave activation over basic carbon catalysts.

work, the use of alkali-activated carbons as catalysts led selectively to N-1-heptenyl-2-pyrrolidinone (B) by dehydration of N-α-hydroxiheptanyl-2-pyrrolidinone A (Scheme 1).

Activated carbons have been used to catalyze efficiently organic synthesis, because of their extended surface area, microporous structure, and high degree of surface reactivity [22]. In addition, the inclusion of alkaline promoters on the carbons results in the generation of basic sites on their surfaces [23–26]. Alkaline carbons may also be appropriate solids to selectively catalyze basic reactions. The microwave irradiation, in combination with alkaline carbons provides in very short times and very mild conditions of reactions an interesting reactivity and peculiar selectivity, being an environmentally friendly process: 82% conversion and 100% selectivity in 1 min under microwaves at 600 W (381–388 K) over Na-Norit catalysts. In contrast, 4 h in batch reactor at 307 K are necessary to achieve 79% conversion and 100% selectivity.

2. Experimental

2.1. Catalyst preparation

Three alkaline carbon catalysts (Na-Norit, Cs-Norit and NaCs-Norit) have been prepared by impregnation of a pristine activated carbon RX-1.5-EXTRA Norit with the corresponding aqueous alkaline chloride solution (2 M for monometallic carbons, and 1 M of each metal chloride solution for the bimetallic carbon) 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 Ø < 0.140 mm diameter.

2.2. Catalyst characterization

The alkali-loaded catalysts Na-Norit, Cs-Norit and the bimetallic NaCs-Norit were characterized following different physicochemical techniques. The pH measures of the catalysts were calculated by aqueous suspensions of the carbon samples, 1 g portions of carbon were mixed with 20 cm^3 of distilled water; the suspensions were shaken mechanically for 48 h at 298 K and then their pH values were determined using a glass electrode, Omega pH-meter, model PHB-62 [27].

Specific surface areas and adsorbed volume of the carbon samples were determined by N_2 adsorption isotherms at 77 K applying the BET method [28] and CO_2 adsorption at 273 K applying Dubinin–Radushkevich and Dubinin–Astakhov methods [161] in a Micromeritics ASAP 2010 Volumetric System. The samples were pre-treated in situ under vacuum at 573 K for 8 h. Volume adsorbed in the different types of pores was calculated by the DFT (Density Functional Theory) method [29] by means of DFT plus software. Thus, carbon dioxide adsorption allows to determine the volume of narrow micropores of the samples while nitrogen adsorption supplies the total volume of the micropores.

To study the thermal stability of the pristine support (activated Norit carbon RX-1.5) and the alkali-Norit catalysts (Na-Norit, Cs-Norit and NaCs-Norit), thermogravimetric analysis (TG) and differential thermal analysis (DTG) were carried out in inert atmosphere (He, 100 cm^3/min) from room temperature to 1000 °C with a heating ramp of 1 °C/min. The thermal analysis instrument SDT Q600 was coupled to a mass spectrometer cuadrupolar Balzers THERMOSTAR (TG-DTG-MS) registering qualitative and quantitatively the gases released during the analysis of each sample. The ash contents of the catalysts were also obtained by using these techniques. For this, the experiments were carried out flowing air (100 mL/min) from room temperature to 1000 °C with a heating ramp of 5 °C/min.

The chemical state and the relative dispersion of the alkali metals deposited on the surface of the carbon of the samples were determined by X-ray photoelectron spectroscopy (XPS). Photoelectron spectra (XPS) were acquired with a VG ESCALAB 200R spectrometer equipped with a hemispherical electron analyzer and MgKα ($h\nu = 1253.6$ 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 C 1s, O 1s, and Na 1s or Cs 3d5/2 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 contents in carbon, hydrogen, and nitrogen of the activated Norit carbon and of the alkali-Norit carbon catalysts were determined by elemental analysis using the atomic absorption spectroscopy with a Microanalyzer Perkin Elmer CHN 2400 equipment.

The basic carbons were also characterized by XRD using a Seifert C-3000 diffractometer with radiation Cu Kα ($\lambda = 0.154$ nm) and by using inductively coupled plasma mass spectrometry (ICP-MS) using a equipment Elan 6000 Perkin-Elmer Sciex with autosampler AS91, a Millipore water purification system Milli-Q Element and a microwave oven Milestone ETHOS PLUS for the digestion of the samples. The ICP-MS technique allows to analyze qualitatively and quantitatively the presence of trace metals.

TPD experiments were performed in a continuous flow apparatus, at atmospheric pressure, using a flow of 20 mol% CO_2 in helium. Prior to adsorption, each sample (ca. 300 mg) was kept under helium flow, at 623 K, until the complete removal of the adsorbed impurities. The sample was cooled down to 298 K and, using a sampling valve, pulses of the adsorbing gas were introduced. The physisorbed gas was removed by passing helium for 30 min. The thermodesorption was then performed by heating the sample at 10 K/min under helium flow (1 mL/s).

The basicity of the alkali carbon catalysts was also studied by using the Knoevenagel probe reaction 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, $pK_a = 16.5$). The reaction was carried out in a batch reactor using three different reaction temperatures (393, 413 and 433 K).

2.3. Reaction procedure

2.3.1. Microwave activation

Activity and selectivity of the catalysts under microwave activation were determined using a multimode microwave oven. The reaction was carried out in a sealed microwave PTFE Teflon vessel. The microwave equipment employed in this work is a SAMSUNG M-1827-N multimode microwave oven operated at the fixed-frequency of 2450 MHz.

The gamma-lactam 2-pyrrolidinone (2 mmol) and the alkali carbon (10 wt%) were blended in the Teflon vessel and an equimolecular amount of 1-heptanal was added in absence of any solvent. The mixture was irradiated in the microwave oven at 600 W of power for 1–5 min. The temperature during the reaction was measured through the Teflon vessel walls using an infrared probe, Ventix 8889, range T −40 to +500 °C, $\lambda = 670$ nm, laser pointer, response time 500 ms. The reaction was followed using an Agilent 6890 gas chromatograph (GC) equipped with a 60 m long BP1 capillary column. The mass spectra of the products were obtained on a Hewlett-Packard HP5971A spectrometer. The reactivity is expressed in terms of the amount of B obtained in wt%. After cooling, the reaction products were extracted with acetone (20 mL) and filtered. The isolated catalyst was then washed with acetone and distilled water and dried at 150 °C for 2 h to be reused in a new cycle of reaction.

2.3.2. Conventional thermal heating

A mixture of gamma-lactam 2-pyrrolidinone and 1-heptanal was heated in a batch reactor while stirring and in absence of any solvent. After five minutes, the catalyst was added to the reaction mixture and the reaction time started. After cooling, the reaction products were extracted with acetone (20 mL) and filtered. The reaction was followed by gas chromatography–mass spectrometry (GC–MS). The reactivity is expressed in terms of the amount of B obtained in wt%.

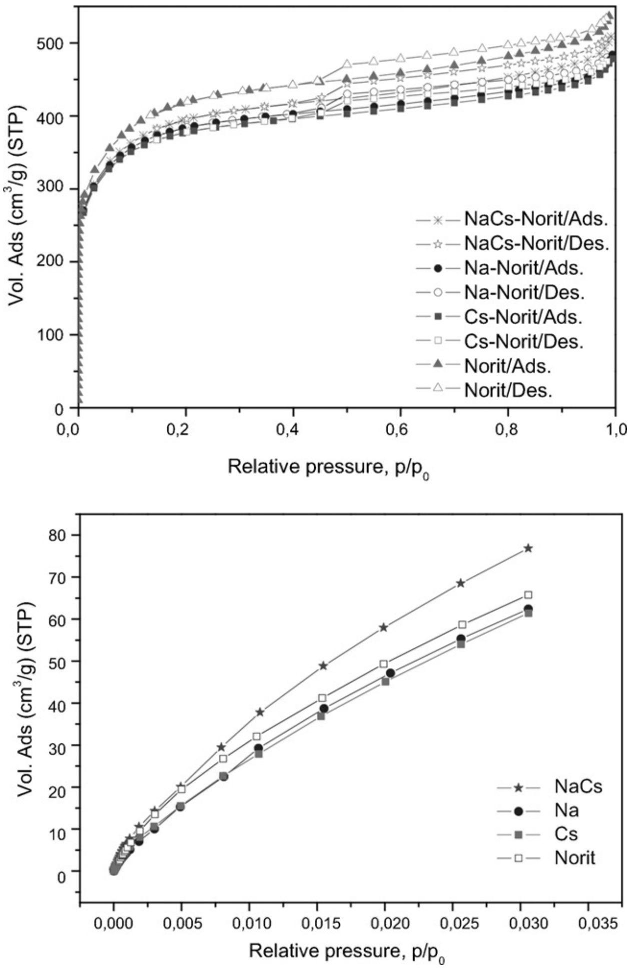

Fig. 1. N_2 adsorption isotherms at 77 K and CO_2 adsorption isotherms at 273 K of the Norit support and the alkali-Norit catalysts (Na-Norit, Cs-Norit and NaCs-Norit).

3. Results and discussion

3.1. Catalyst characterization

Fig. 1 illustrates the nitrogen adsorption isotherms at 77 K and CO_2 adsorption isotherms at 273 K. It must be emphasized that the main characteristic of an activated carbon, apart from its high surface area, is its microporosity. The analysis of the gas adsorption isotherms in activated carbons provides a first approximation to their microporous structure employing adsorbants such as nitrogen (77 K) and carbon dioxide (273 K). It has been verified that carbon dioxide adsorption allows the determination of the volume of narrow micropores while nitrogen adsorption supplies the total volume of the micropores. Table 1 shows specific surface areas (BET) and distribution of the pore volume obtained from nitrogen adsorption at 77 K for the samples. The Norit pristine carbon has a high specific surface area (1450 m^2/g) with a total adsorbed volume of nitrogen of 0.571 cm^3/g (Table 1). The pore size distribution of this carbon is principally micropores (81.8%) with an important contribution of mesopores (16.5%). The impregnation of the pristine carbon with different alkali chlorides does not change significantly the specific surface area characteristics of the support (Table 1). The catalysts show slight differences in the total volume of micropores. The Cs-Norit catalyst presents the higher value of surface area and nitrogen adsorption into the micropores. To study the narrow microporosity in solids by CO_2 adsorption, different equations can be used, being the Dubinin–Radushkevich (D–R) equation the most frequently used [30]. When the microporous structures are not homogeneous, the Dubinin–Astakhov (D–A) equation is used [30]. Table 1 shows the values of the microporous area and the volume of the micropores calculated using both equations, D–R and D–A. It can be verified from these results that the microporous

Table 1

(a) BET specific surface areas and distribution of the pore volume obtained from N_2 adsorption at 77 K and (b) microporous area and volume of micropores obtained from CO_2 adsorption at 273 K for the pristine Norit carbon and the alkali-Norit carbons.

Catalyst	N_2 adsorption				CO_2 adsoprtion			
	S_{BET} (m^2/g)	$V_{micropore}$ (cm^3/g)	$V_{mesopore}$ (cm^3/g)	V_{tot} (cm^3/g)	$S_{micropore(D–R)}$* (m^2/g)	$V_{micropore(D–R)}$* (cm^3/g)	$S_{micropore(D–A)}$* (m^2/g)	$V_{micropore(D–A)}$* (cm^3/g)
Norit	1450	0.467 (81.8%)	0.094 (16.5%)	0.571	554	0.201	683	0.272
Na-Norit	1375	0.440 (77.2%)	0.111 (19.5%)	0.570	300	0.109	255	0.092
Cs-Norit	1447	0.460 (84.7%)	0.074 (13.6%)	0.543	370	0.135	363	0.135
NaCs-Norit	1338	0.434 (78.2%)	0.104 (18.7%)	0.555	460	0.167	508	0.192

* Calculations were carried out using the Dubinin–Radushkevich (D–R) equation and the Dubinin–Astakhov (D–A) equation with the data obtained from CO_2 adsorption.

Table 2
Ph, thermogravimetric analysis (TG), elemental analysis and quantitative elemental analysis (ICP-MS) of the carbon catalysts.

Catalyst	pH	Ash (%)	M_2O[a]	Metal (at-g/100 g cat)	%C	%H	%N	%O	Analyte concentration (ppm)	
									Na	Cs
Norit	7.05	4.3	–	–	90.50	0.38	0.45	4.37	305.17 (0.030%)[b]	1.58 (0.0002%)[b]
Na-Norit	7.17	5.1	0.8	0.013	88.82	0.52	0.45	5.11	602.26 (0.06%)[b]	0.39
Cs-Norit	7.58	5.2	0.9	0.003	87.94	0.60	0.47	5.79	478.95	790.40 (0.08%)[b]
NaCs-Norit	7.51	5.4	1.1	–	89.12	0.50	0.46	4.52	554.91 (0.05%)[b]	407.78 (0.04%)

[a] Difference (ash content), M – Alkali metal.

[b] The values enclosed in brackets represent weight percentage of the correspondent analyte.

specific surface area of the support decreases when it is impregnated with the corresponding alkali salt as the metallic cations (Na^+, Cs^+) deposit on the microporous surface of the carbon.

From Fig. 1 it can also be appreciated that the adsorption of CO_2 at 273 K is lower than the adsorption of nitrogen at 77 K. This indicates the absence of narrow micropores in the structure of the solid catalysts prepared. The CO_2 adsorption isotherms of the NaCs-Norit catalysts show a higher adsorption of CO_2 than the rest of the catalysts because the metallic cations mostly deposit on the surface during the impregnation, without entering the microporous structure of the carbon. These results were contrasted using other techniques, such as XPS, the results are shown below.

Table 2 summarizes the pH of the alkali-doped activated carbons catalysts (Na-Norit, Cs-Norit and NaCs-Norit). The pristine carbon, RX-1 EXTRA Norit, exhibits a pH of 7.05, which increases only slightly in the sample supported with sodium or/and cesium respectively in the range 7.17–7.51.

The thermal analysis (TG-DTG-MS) obtained for the alkali-Norit catalysts and the pristine Norit carbon, showed similar profiles when they were under heating process in inert atmosphere. The alkali-Norit catalysts showed a higher loss in weight than the pristine Norit support (Norit, 6.94%; Na-Norit, 8.85%; Cs-Norit, 8.01%; NaCs-Norit, 8.40%) taking into account the decomposition of the new oxygenated surface groups which were formed during the manipulation of the samples as a consequence of the reoxidation of the carbon surface, as well as the formation of the oxide and carbonate species form in the structure of the carbon during the impregnation. Fig. 2 shows the spectra for the pristine support and one of the carbon catalysts prepared, Cs-Norit. The weight losses below 500 °C approximately can be principally attributed to carbon dioxide and water. The weight loss as water is normally due to the water adsorbed on the surface during the manipulation of the samples. If the weight loss happens at temperatures higher than 100 °C, then it is related with the dehydration of alcohol and phenol groups that are present on the surface of the carbon. The thermograms obtained for the samples show that below 100 °C the weight loss was due to CO_2 and H_2O molecules enclosed in the porous structure of the carbon. The more sensitive surface oxygenated groups were removed at temperatures below 300 °C approximately, and they included acidic groups such as carboxiles, lactones and anhydrides [31,32]. The weight loss that occurred approximately at temperatures above 700 °C was attributed to a loss of oxygenated surface groups with a weak acidic, neutral or basic character such as ether, phenol, carbonyl, quinone and pyrone groups. It could also be due to a rupture in the molecular structure of the carbon by expulsion of gases such as hydrogen, carbon dioxide and hydrocarbons. At temperatures higher than 1000° C, it can be affirmed that practically all the oxygenated surface groups have decomposed [33].

Table 2 shows the results obtained from the thermogravimetric analyses of the samples calcined in air flow (100 mL/min) at 1000 °C. The Norit carbon sample showed content in ash of 4.3%; this content in ash was higher in the alkali-Norit carbon samples. The difference in the content of ash of the impregnated carbons and the pristine carbon without treatment was used to calculate the percentage of the corresponding alkali metal supported in each catalyst. The results 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 Cs^+ ions has to overcame to access the interior of the micropores of the carbon support.

The chemical state and the relative dispersion of the alkaline metals at the surface of the carbon of the different samples were determined by XPS. Table 3 shows the BEs of C 1s and O 1s core levels, and the characteristic inner levels of the alkaline elements, together with the M/C atomic ratios, determined from the peak intensities and the tabulated sensitivity atomic factors [34]. Generally, all the samples showed that the C1s core level presented three peaks; the first peak at 284.5 eV due to the $\rangle C{=}C\langle$ bonds of the

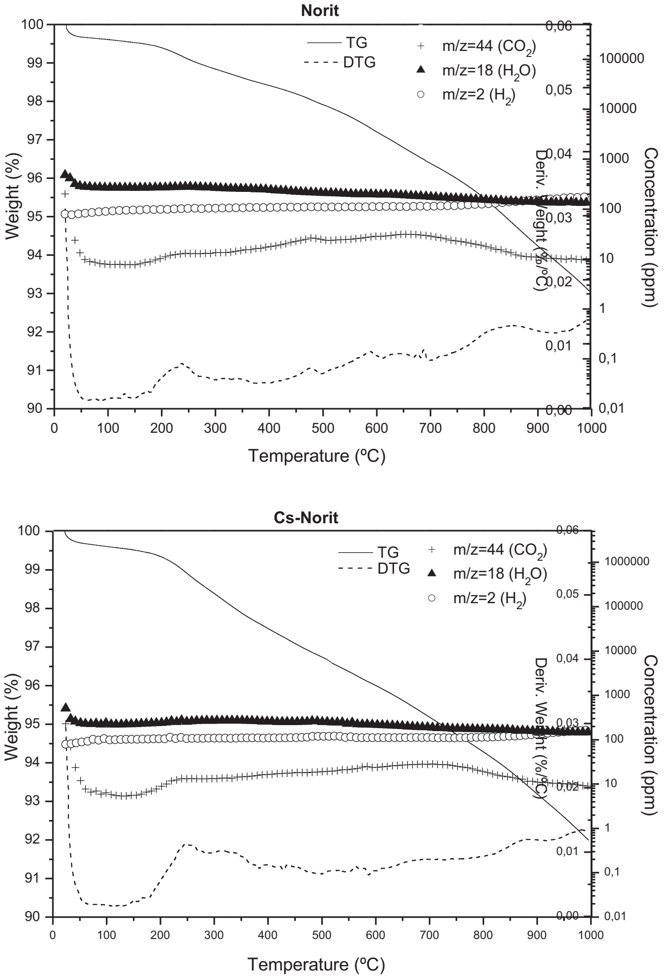

Fig. 2. Thermograms obtained by thermal and mass analysis (TG-DTG-MS) of the pristine Norit carbon and Cs-Norit catalyst. Heating ramp: 1 °C/min until 1000 °C, He flow = 100 mL/min.

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

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

The values in parentheses indicate the % of each peak.
[a] No sodium was detected.

carbon structure or to the non-functionalized —CH— species which still conserved hydrogen atoms, the second peak approximately at 285.9 eV showing approximately a 25–39% contribution to the total area due 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 nature of the oxygenated surface groups that were present on the carbon surface of the samples was determined through the values of the bond energies of core level O1s. 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 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 the samples. The O_{total}/C_{total} relation is showed in Table 3, which indicated the degree of oxidation of the surface of the samples. 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.

Table 3 also shows the concentration of the alkali elements that were incorporated in the activated Norit carbon used to prepare the alkali-Norit samples. In order to calculate this, the intensities of the peaks, corrected by the atomic sensitivity factors, were measured. The results show 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 micropores 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 micropores, is higher, and therefore they tend to stay on the surface. It was not possible to detect Na$^+$ on the surface of the carbon for the Na-Norit sample 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. Although Cs-Norit sample 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.

The results obtained by atomic absorption spectroscopy are shown in Table 2. From these results and knowing the ash content in the samples by thermal analysis (Table 2), the amount of oxygen in each sample was calculated by subtraction. Generally, the percentage in oxygen increased slightly in the impregnated carbon samples compared to the pristine Norit carbon. This increase was due to the presence of a higher number of oxygenated surface groups in the carbon structure of the alkali-Norit catalysts as a consequence of a reoxidation of their surface during their manipulation.

The X-ray diffraction spectra (XRD) of the Norit support and the basic alkali-Norit carbons are illustrated in Fig. 3. X-ray diffraction and the diffraction patterns from the JCPDS (Joint Committee on Powder Diffraction Standards) of the ICDD (International Center

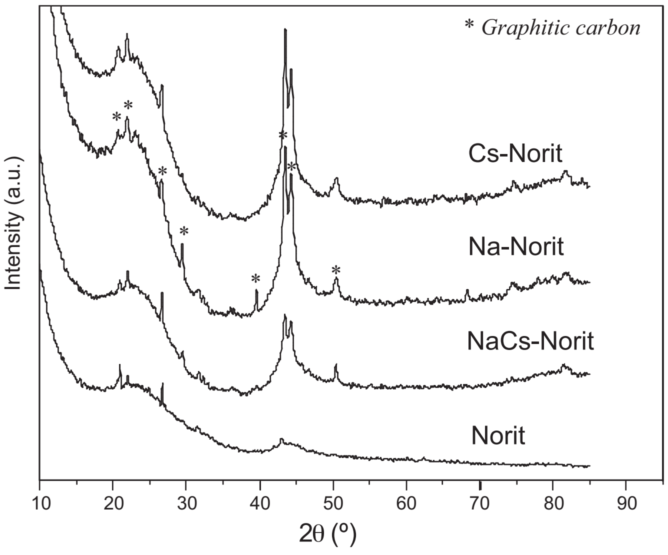

Fig. 3. XRD of the Norit support and Na-Norit, Cs-Norit, NaCs-Norit carbon catalysts.

for Diffraction Data), did not show the presence of alkali chlorides in the structure of the carbon, which could have stayed in the structure after impregnating the pristine Norit support during the preparation of the alkali-Norit samples. The XRD diffractogram corresponding to the pristine Norit support showed very low intensity peaks corresponding to graphitic carbon. After impregnating the pristine Norit support, the XRD spectra of the Na-Norit, Cs-Norit and NaCs-Norit samples showed no additional peaks corresponding to carbonate and/or metallic oxide species, as they were by XPS.

The ICP-mass technique was used to characterize both qualitatively and quantitatively the inorganic species (trace metals) present in the pristine Norit as well as in the alkali-Norit carbons (Na-Norit, Cs-Norit and NaCs-Norit). The results obtained in the quantitative analysis of metals Na and Cs involved in the preparation of the basic carbon catalysts are shown as analyte concentration (ppm) in Table 2. The qualitative analysis of the samples show the presence of trace metals such as B, Mg, Al, K, Ca, Fe, Ti, Bi, V, Mn, Zn and Ba.

Fig. 4 shows the TPD profiles of the pristine Norit carbon and the alkali-Norit samples. For the pristine carbon a “shoulder” at 570 K was detected due to the decomposition of superficial groups. For Cs-Norit and NaCs-Norit catalysts, a band in the range 350–550 K was detected and this band is stronger in case of Cs-Norit catalyst. For NaCs-Norit catalyst, a “shoulder” in the range 550–750 K was also detected. For Na-Norit catalyst, a weak “shoulder” in the range 600–800 K was detected. The deconvolution of these curves showed that three types of basic sites might be considered: weak (420 K), medium strength (500 K) and strong basic sites (700 K). It can be concluded that Cs-Norit is mainly composed by weak basic sites, NaCs-Norit shows both weak and strong basic sites and Na-Norit presents strong basic sites. Considering the activity results obtained in the studied reaction for all the samples, the activity of the reaction can be assigned to weak basic sites present mostly in Cs-Norit catalysts and lesser in NaCs-Norit catalysts.

The basicity probe reaction of Knoevenagel condensation showed that most of the active sites in the alkaline promoted carbons have basic strength between $9 \le pK_a \le 13.3$ and a few of them between $13.3 \le pK_a \le 16.5$ (Fig. 5).

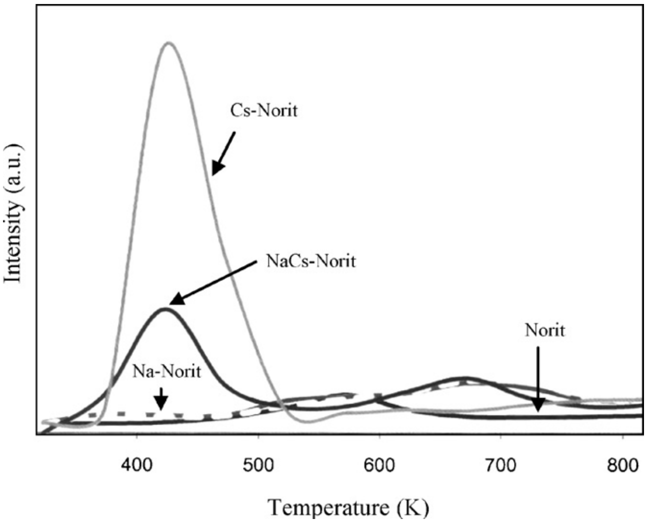

Fig. 4. TPD-CO_2 analysis of the carbon catalysts.

3.2. *Synthesis of N-substituted-gamma-lactams under microwave irradiation*

Under our experimental conditions basic catalysis and microwave activation, 2-pyrrolidione reacts with 1-heptanal at the N-position (Scheme 1). The mass spectrum of the reaction product confirms that N-substituted-gamma-lactam of type B, N-1-heptenyl-2-pyrrolidinone, is selectively obtained (MS m/s: 182 (M^+), 125, 97, 87, 70, 57, 42). As we have shown previously, the nature of the products in this reaction depends upon the choice of the catalyst type. Alkaline-promoted carbons are appropriate materials to catalyze basic organic reactions showing basic sites with strength up to $pK_a = 16.5$ [29]. Considering that the NH group of 2-pyrrolidinone presents a $pK_a = 11.3$ [10], these basic carbons are appropriate catalysts to perform the N-substitution (Scheme 1).

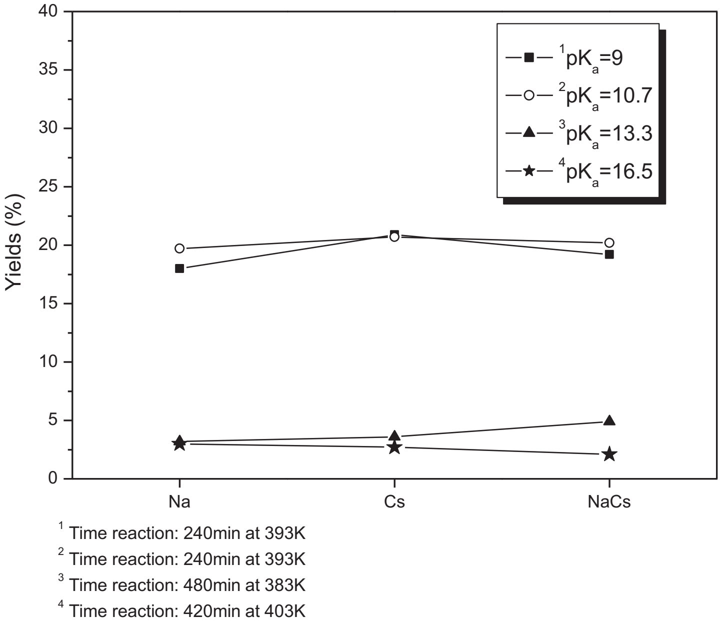

Fig. 5. Catalytic activity measurements of the activated carbon-supported catalysts obtained by Knoevenagel basicity test reaction of benzaldehyde with methylenic compounds (1:1) (ethyl cyanoacetate, $pK_a = 9$, 240 min at 393 K; ethyl acetoacetate, $pK_a = 10.7$, 240 min at 393 K; diethyl malonate, $pK_a = 13.3$, 480 min at 383 K; ethyl bromoacetate, $pK_a = 16.5$, 420 min at 403 K).

Table 4
Kinetic constants for the C—N coupling reaction of 2-pyrrolidinone with 1-heptanal assisted by microwave irradiation (600 W, 5 min) using basic carbon catalysts.

Catalyst	Power (W)	T (K)	k ($\times 10^2$ M^{-1} s^{-1} g^{-1}_{cat})	k ($\times 10^5$ M^{-1} s^{-1} m^{-2})
Norit	600	[a]381–388	0.36	0.25
Na-Norit	600	[a]381–388	19.4	13.9
Cs-Norit	600	[a]381–388	21.2	15.5
NaCs-Norit	600	[a]381–388	17.2	12.2

$[\text{2-pyrrolidinone}]_{t=0}$ = 7 M; $[\text{1-heptanal}]_{t=0}$ = 7 M.

[a] Reaction time: 5 min at 600 W.

3.2.1. *Kinetic study*

Scheme 1 shows the carbon–nitrogen coupling of 2-pyrrolidinone and 1-heptanal. It is supposed that the basic carbon catalyst abstract the proton of the NH group from the lactamic ring (pK_a = 11.3 [10]). Then, the C—N coupling is produced by the nucleophilic attack of the lactamic anion to the carbonyl group of the aldehyde forming the adduct **A**. However, the adduct (**A**) formed here is unstable and it is stabilized by losing a water molecule leading to the final product, N-1-heptenyl-2-pyrrolidinone (**B**). The reaction proceeds with 100% selectivity to N-1-heptenyl-2-pyrrolidinone under all reaction conditions. The reported selectivity was determined in the following way [yield of desired product]/([yield of detected product] + [detected reactant]). The total balance calculated to carbon atoms was in all cases better than 98%.

Considering that the reaction is equimolar, the integrated rate expressions for the proposed first and second order kinetic models were simplified as shown next:

First order; $r = k$[2-pirrolidinona]

$$\ln[A] = -k(t) + \ln[A_0];\ \ln[A_0(1-x)] = -k(t) + \ln[A_0]$$

Second order; $r = k$[2-pirrolidinona][1-heptanal]

$$1/[A] = k(t) + 1/[A_0];\ 1/[A_0(1-x)] = k(t) + 1/[A_0]$$

where $[A_0]$ is the initial concentration of 2-pyrrolidinone, x represents the conversion of the product B, $A_0(1-x)$ is the concentration of 2-pyrrolidinone which has not reacted, and t is the reaction time. A first order or exponential kinetic would fit the experimental data ln [2-pyrrolidinone] versus time to a line with slope k, while a second order or hyperbolic kinetic would fit the experimental data 1/[2-pyrrolidinone] versus time to a line with slope k. In this case, for the equimolecular reaction between 2-pyrrolidinone and 1-heptanal, a higher linear correlation coefficient was obtained when representing ln [reactant] versus time, confirming that the proposed reaction followed a first order kinetic where the rate determining step of the reaction was the abstraction of the proton by the basic carbon. Table 4 shows the kinetic constants calculated for the different catalysts. From these results it can be said that the rate constants decrease in the order: Cs-Norit > Na-Norit > NaCs-Norit > Norit.

Under our experimental conditions, the reaction was neither controlled by external nor internal diffusion. This experiment was carried out by using different particle sizes of the catalysts (0.074, 0.140 and 0.250 mm) and different stirring rates (600 and 1500 rpm). Under these reaction conditions, no considerable change in catalytic activity was detected.

3.2.2. *Influence of alkali promoter in the supported catalysts*

The influence of the metal supported on the catalyst was studied for the reaction between 2-pyrrolidinone and 1-heptanal where it was evident that the activity in reaction of the pristine Norit carbon increased once it was impregnated with the corresponding alkali salts (Table 5). The results obtained showed the following order in activity: Norit < NaCs-Norit < Na-Norit < Cs-Norit. Thus, conversions of 72% and 100% selectivity are reached in only 5 min of reaction when Cs-Norit is the catalyst. Closer conversions (around 69% and 100% selectivity for Na-Norit and 64% and 100% selectivity for NaCs-Norit) are obtained when the catalyst is doped with Na.

It is expected that the basic properties of carbon catalysts have a particular influence on the activity and selectivity of the C—N coupling reaction. The thermogravimetric analysis data showed in Table 2 indicate that the metal content diminishes when the size of the alkaline cation increase as a consequence of the greater difficulty in accessing inside the pores in case of cesium than in case of sodium. In addition, the XPS results showed slight cesium enrichment at the surface while sodium was not detected at the surface. Cs-Norit sample exhibited higher activity in the reaction than the rest of samples indicating the better effectiveness as catalyst. Kinetic studies of the reaction confirm the proposed theory and Cs-Norit showed the highest values of kinetic rate constants. These results clearly show that basic strength of active site play dominant role in this reaction. This is clearly valid under both thermal as well as microwave conditions.

3.2.3. *Other examples of microwave assisted synthesis of N-substituted-gamma-lactams over alkali carbon catalysts*

We also study the synthesis of other N-substituted-gamma-lactams by using 2-pyrrolidinone and 2-indolinone as gamma-lactams, and 1-heptanal and 1-octanal as substituent agents. To carry out the reactions an equimolar mixture (2 mmol) of the reactants and Cs-Norit catalyst (10 wt%) was irradiated under microwaves at 600 W for 5 min. When 2-pyrrolidinone and 1-octanal were employed yields of 49% were reached versus 72% obtained when 1-heptanal was used as substituent agent. The use of 2-indolinone as gamma-lactam and 1-heptanal as aldehyde, decreases the final conversion values up to 36% due to the major steric impediment as occurs in the reaction between 2-indolinone and 1-octanal where yields of 28% were reached.

Table 5
Carbon–nitrogen coupling reaction between 2-pyrrolidinone and 1-heptanal under microwave activation in presence of alkali-Norit catalysts (t = 5 min at 600 W).

	Catalyst			
	Norit[b]	Na-Norit[b]	Cs-Norit[b]	NaCs-Norit[b]
Conversion (%)[a] $_{t=5\,\text{min},\,600\,\text{W}}$	1.7	68.8	72.0	64.4

Equimolar amount of 2-pyrrolidinone and 1-heptanal (2 mmol).

[a] Amount of catalyst: 0.02 g.

[b] 100% selectivity to N-1-heptenyl-2-pyrrolidinone.

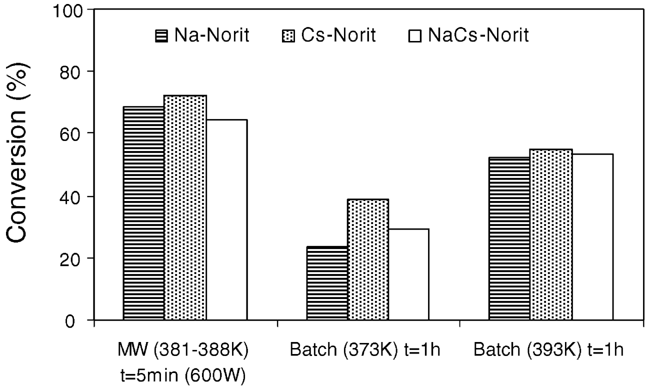

Fig. 6. Microwave activation versus conventional thermal activation (batch) in the N-substitution of 2-pyrrolidinone with 1-heptanal catalyzed by basic carbons.

3.2.4. Microwave activation versus conventional thermal activation

The reaction carried out under conventional thermal activation in a batch reactor when using equimolar amounts of reactants was negligible. Therefore, the reaction between 2-pyrrolidinone and 1-heptanal was carried out using an excess of the aldehyde (1-heptanal, 7.00 mmol) at temperatures of 373 and 393 K over Na-Norit, Cs-Norit and NaCs-Norit catalysts. The excess of 1-heptanal not used during reaction was filtered and then recycled.

Fig. 6 shows conversions obtained at 373 and 393 K in 4 h in a batch reactor. From these results it can be concluded that under conventional thermal activation (batch) all carbon catalysts were active in the C—N coupling reaction between 2-pyrrolidinone and 1-heptanal using an excess of aldehyde. An increase in the reaction temperature resulted in an increase of the conversion maintaining the selectivity (100%) to N-1-heptenyl-2-pyrrolidinone.

Fig. 6 also compared the results obtained under conventional thermal activation (373–393 K) with those obtained under microwave activation in a close range of temperatures (381–388 K). These results proves how efficient is microwave activation (5 min, 60 < conversion(%) < 70, 100% selectivity) versus conventional thermal activation (1 h, 30 < conversion(%) < 50, 100% selectivity). Anyway, 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 significant changes in the final yield of the reaction (Fig. 7).

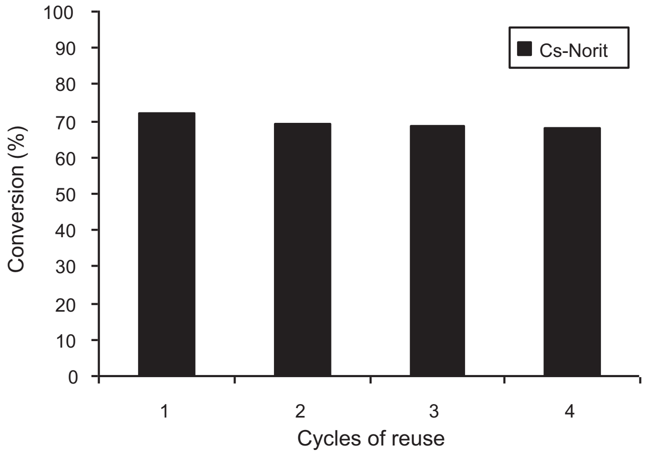

Fig. 7. Cycles of reuse of Cs-Norit catalyst in the microwave activation of 2-pyrrolidinone with 1-heptanal ($t = 5$ min, 600 W).

Table 6
TOF for carbon–nitrogen coupling reaction between 2-pyrrolidinone and 1-heptanal under microwave (600 W, 5 min) and conventional thermal (373 and 393 K, 1 h) activation in presence of alkali-Norit catalysts.

TOF (s^{-1})	Catalyst		
	Na-Norit	Cs-Norit	NaCs-Norit
MW (381–388 K)[a]	0.029	2.40	0.358
Batch (373 K)[b]	0.006	0.108	0.013
Batch (393 K)[b]	0.014	0.153	0.025

[a] 600 W, $t = 5$ min.
[b] $t = 1$ h.

Knoevenagel probe reaction results demonstrated that carbon catalysts contain basic sites strong enough to perform the N—C coupling reaction between 2-pyrrolidinone and 1-heptanal. Table 6 presents TOF data for the studied reaction. The results in this table show that Cs-Norit catalyst displays the highest TOF value under microwave and conventional thermal activation than Na-Norit and NaCs-Norit catalysts. This suggests that Cs-Norit is basic enough to carry out the reaction proving to be the most effective catalyst.

4. Conclusions

The effect of microwaves in the activation of alkaline promoted carbons has been explored in the N-substitution of 2-pyrrolidinone with 1-heptanal to obtain N-substituted-gamma-lactams for the synthesis of important neuroexcitatory pharmaceuticals. Enhancement effect on the reaction rate by combining the basicity of the carbon catalysts and microwaves is presented as an alternative method for the selective construction of C—N bonds in the synthesis of N-1-heptenyl-2-pyrrolidinone derivatives. It was also found that there is a substantial enhancing effect in the yield when microwave irradiation was used to activate the reaction instead of the conventional thermal activation methods. This process can be also generalized for the production of similar fine chemicals due to the mild conditions that this system offers. In addition, although a large body of work dealing with microwaves activation, only a relatively small number of papers report the influence of the reaction conditions on the rate and yields of chemical reactions. It is important that those parameters are fine tuned and controlled to maximize the microwave effects. We have found that among all the experimental procedures induced by heterogeneous media employed for the synthesis of numerous chemical compounds, the combination of microwave irradiation with alkaline carbons offers interesting prospects because excellent yields can be achieved under very mild conditions.

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