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Catalytic properties of alkali metal-modified oxide supports for the Knoevenagel condensation: Kinetic aspects

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ABSTRACT

The characterization of the alkali-modified metal oxides surface basicity by condensation of benzaldehyde with some methylenic compounds (ethyl cyanoacetate, ethyl acetoacetate and diethyl malonate) as test reaction were studied with a series of lithium, sodium, potassium, rubidium and cesium impregnated simple oxide matrices (SiO_2, Al_2O_3, $Nb_2O_5{\cdot}nH_2O$ and Nb_2O_5). The condensation of benzaldehyde and other substituted benzaldehydes with ethyl acetoacetate using these catalysts and in absence of any solvent, is also proposed as a "green method" in the preparation of pharmaceuticals in the line of calcium channel blockers and antihypertensives. The role of the support nature in the Knoevenagel condensation activity is considered.

1. Introduction

In the production of Fine Chemicals, the development of environmentally friendly solid catalysts has known a recent growing interest. Base catalysed processes such as aldolisation, alkylation, Knoevenagel condensation and Michael addition are commonly used for the manufacture of these chemicals. A better preservation of environment would require the substitution of liquid bases and organometallics by solid catalysts. Indeed solid catalysts have many advantages from the technical point of view: they present fewer disposal problems, while allowing easier separation and recovery of the products, catalysts and solvent if any. They are non-corrosive, and offer environmentally benign and more economical pathways for the synthesis of fine chemicals.

In the literature, several solid catalysts with basic properties have been proposed. There are catalysts mainly based on alkali metals supported on matrix having high surface area such as zeolites, mesoporous molecular sieves [1], oxides, mixed oxides and doped oxides [2,3]. Most of the papers are devoted to cesium oxide supported on metal oxides, or zeolites, or mesoporous matrices. However, there are few studies of these supports modified with all alkali metal elements.

Different reactions have been studied on solid bases. In particular, the kinetic study of Knoevenagel condensation has been used to measure the total amount of basic sites and the basic strength distribution in solid catalysts. This reaction can also be used to form C–C bonds through the reaction of a carbonyl with an active methylenic group [4]. It is widely used in the synthesis of important intermediates or end-products for perfumes [5], pharmaceuticals [6], calcium antagonists [7], and polymers [8].

In the present work, we have used the Knoevenagel condensation as probe reaction to study the basicity and reactivity of a series of alkali-modified metal oxides, which have been prepared by impregnation with alkali metal acetates. We have chosen three types of oxides (SiO_2, Al_2O_3, hydrated and dehydrated Nb_2O_5), which present various acidities and therefore give rise to the different strength of interaction with alkali metals. The acidic–basic properties of these materials were previously tested in the cyclisation of acetonylacetone, decomposition of isopropanol and hydrosulphurisation reaction [9]. The modification of niobia supports (hydrated and dehydrated) with alkali metal species creates acid–base catalysts highly selective in the methanethiol production, whereas the impregnation of silica and alumina with these species leads to the generation of basicity [9].

We have also employed the Knoevenagel condensation to prepare compounds of the type A, which are intermediates in the preparation of some dihydropyridines of type B (Scheme 1). Dihydropyridines chemistry is of interest not only from point of view of fundamental research on heterocyclic compounds [10], but especially because of expanding practical applications of

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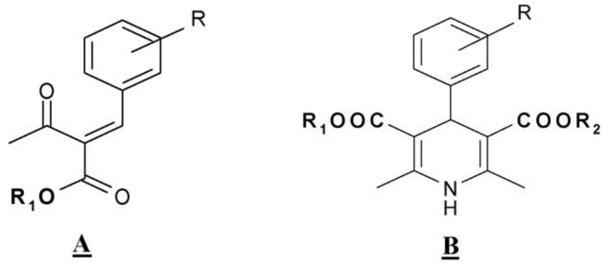


Scheme 1. Structure of the intermediate for the synthesis of 1,4-dihydropyridines (compound of type A), and general structure of 4-aryl-1,4-dihydropyridine derivatives (compound of type B).

1,4-dihydropyridine derivatives as pharmaceuticals in the line of calcium channel blockers [11,12].

2. Experimental

2.1. Catalysts preparation

Acetates of alkaline metals (Li, Na, K, Rb or Cs) were deposited onto SiO_2 (Ventron, 365 m^2/g), Al_2O_3 (Sasol, 190 m^2/g) and $Nb_2O_5 \cdot nH_2O$ (CBMM, Brazil, 30 m^2/g) by the incipient wetness impregnation method to prepare three series of catalysts. The outgassed SiO_2, Al_2O_3 and $Nb_2O_5 \cdot nH_2O$ (373 K, 2 h in the oven) were filled in with the appropriate amount of an aqueous solution of acetate (CH_3COOLi, CH_3COONa, CH_3COOK, CH_3COORb or CH_3COOCs, Aldrich, a volume of the solution ideally equal to the pore volume of the support) and located in an evaporator flask, where the catalyst was rotated and heated at 373 K for 1 h. The impregnated powder was dried at 373 K for 18 h and then calcined at 773 K for 10 h in an oven. In such a case we obtained three series of catalysts; X/SiO_2, X/Al_2O_3 and $X/Nb_2O_5 \cdot nH_2O$ (X = Li, Na, K, Rb, or Cs, respectively).

The fourth series of catalysts (X/Nb_2O_5, X = Li, Na, K, Rb, or Cs, respectively) was prepared using $Nb_2O_5 \cdot nH_2O$ as a support but after a different pre-treatment. $Nb_2O_5 \cdot nH_2O$ was dried at 373 K for 5 h and then calcined at 773 K for 10 h in the oven and in the presence of an airflow during 6 h. The calcined support, denoted as Nb_2O_5, was filled in with the appropriate amount of an aqueous solution of the alkaline acetates and located in an evaporator flask, where the catalyst was rotated and heated at 373 K for 1 h. The impregnated powder was dried at 373 K for 18 h and then calcined again at 773 K for 10 h in the oven.

The amount of alkali metal acetate used for the impregnation was calculated for the loading of metal equal to 0.5 mmol/g of the support.

2.2. Characterization of the materials

The texture of the catalysts was characterised using XRD, N_2 adsorption/desorption and infrared spectroscopy in the skeleton vibration region and is reported in [9].

2.3. Reaction procedure: Knoevenagel condensation

An equimolar solution 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 (413–433 K). Then, depending on the active methylenic compound employed, 1%, 2% or 10% of catalyst were added and the reaction time started. Samples were taken periodically, and the evolution of the reaction was followed by GC–MS.

3. Results and discussion

3.1. Characterization

The data calculated from the nitrogen adsorption at 77 K were reported in [9]. In general, the BET surface area of silica and dehydrated niobia significantly decreases after the impregnation with alkali metal acetates followed by the calcination. This is accompanied by the increase of average mesopore diameter and, for silica support, also by a significant growth in mesopore volume. It is not the case of alumina-based materials for which all textural parameters slightly depend on the impregnation procedure an hydrated niobia for which the surface area changes depending on the formation of the new phase via the chemical reaction between the support an alkali medium.

From the XRD and IR studies we have concluded previously [9] that the lack or very weak chemical interaction of the support with the impregnating medium, as in the case of silica, leads to the loading of alkali metal oxides on the support surface an easy migration resulting in the agglomeration of oxide species [9]. Moreover, this loading most probably builds additional porosity, which results in the increase of average mesopore volume and diameter. In the case of the interaction of metal oxide with alumina surface protects the agglomeration of alkali metal species and gives rise to a better dispersion. This provokes the remaining of textural parameters of alumina, almost untouched after impregnation with alkali metal acetates. The chemical reaction between alkali metal salt and hydrated niobia changes the textural parameters of the final materials according to the formation of new mixed phases [9].

3.2. Kinetics and mechanism of the Knoevenagel condensation

The condensation between benzaldehyde and the three active methylenic compounds (ethyl cyanoacetate, $pK_a = 9$; ethyl acetoacetate, $pK_a = 10.7$ and diethyl malonate, $pK_a = 13.3$) were carried out with Li, Na, K, Rb and Cs impregnated simple oxide samples, and with the pristine supports (particle size within 0.074 and 0.140 mm) at 413 K.

The conversion values of benzaldehyde in the Knoevenagel condensation with ethyl cyanoacetate ($pK_a = 9$) using metal oxides modified with alkali metals are shown in Fig. 1(A–D). As it has been found, the selectivity to the Knoevenagel product is 100% so conversions are also the yields of product. Incorporation of the alkali cations significantly increases the activity for alumina and silica supports but decreases the activity of hydrated and dehydrated niobia supports. The order of activity found for the unmodified supports was the following: $Nb_2O_5 \cdot nH_2O > Nb_2O_5 > Al_2O_3 > SiO_2$.

Benzaldehyde has also been condensed with ethyl acetoacetate ($pK_a = 10.7$). The results at 413 K and 300 min time of the reaction are given in Table 1 and the trend followed by the catalysts it is showed in Fig. 2. The activity orders are

Series X/SiO_2: K > Rb ≈ Na > Cs > Li
Series X/Al_2O_3: K > Cs > Rb ≈ Na ≈ Li
Series $X/Nb_2O_5 \cdot nH_2O$: Rb > K > Na > Li > Cs
Series X/Nb_2O_5: Rb > K > Na > Cs > Li

These results indicate that the studied catalysts possess basic sites capable of abstracting protons of $pK_a \leq 10.7$. However, other reaction products are formed, in addition to the Knoevenagel condensation product. Thus, one mole of this last product can condense again with another mole of ethyl acetoacetate to give different products and also the ethyl acetoacetate can suffer

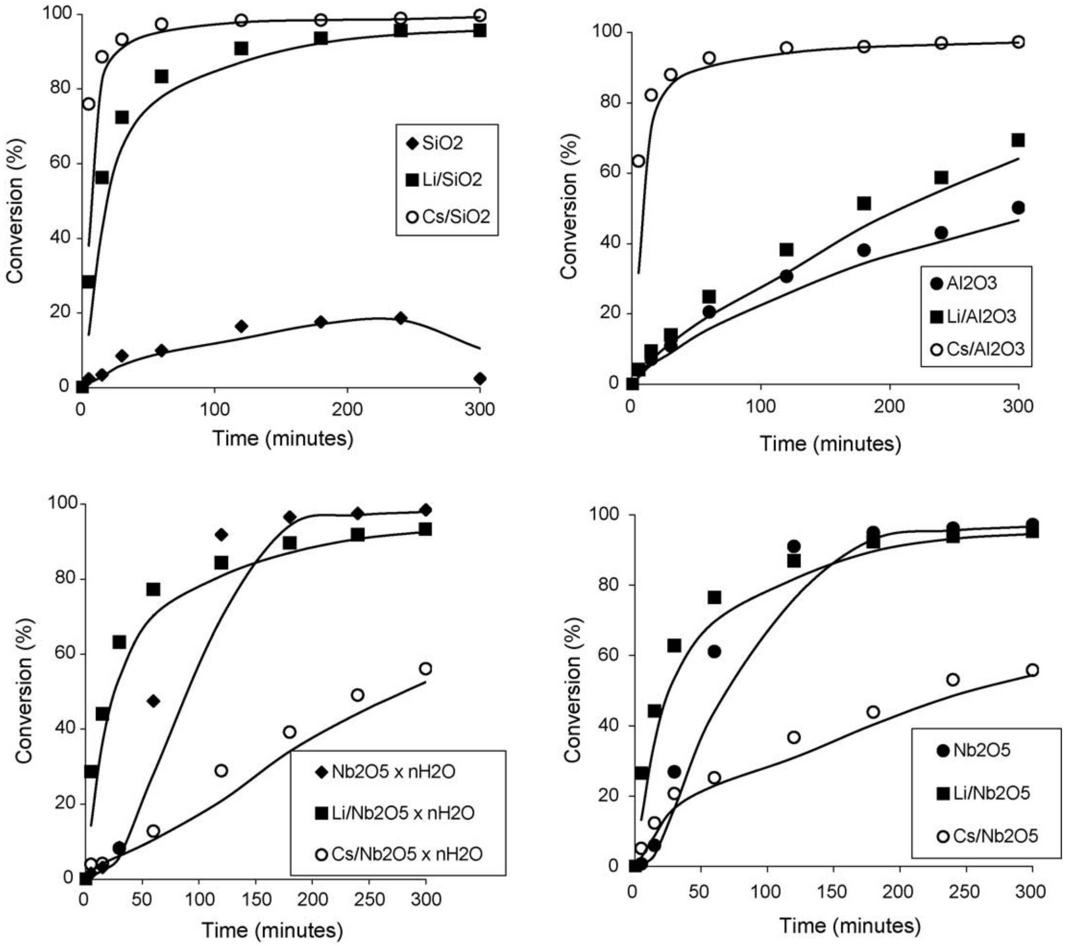


Fig. 1. (A–D) Condensation of benzaldehyde (14 mmol) and ethyl cyanoacetate (14 mmol) at 413 K, using 0.031 g of catalyst (1 wt.%): (A) SiO_2/X, (B) Al_2O_3/X, (C) $Nb_2O_5 \cdot nH_2O$/X and (D) Nb_2O_5/X (X = Li and Cs).

self-condensation [4]. Both products are included as other products in the selectivity column listed in Table 1.

In the condensation of benzaldehyde with diethyl malonate at 403 K ($pK_a = 13.3$) the conversion obtained was very low, indicating that the catalysts have enough strong basic sites able to abstract protons with $pK_a \leq 13.3$ to carry up the reaction.

Table 1

Condensation of benzaldehyde (9 mmol) and ethylacetoacetate (9 mmol) at 413 K using X/SiO_2, X/Al_2O_3, X/$Nb_2O_5 \cdot nH_2O$ and X/Nb_2O_5 (X = Li, Na, K, Rb and Cs) catalysts (0.044 g) during 300 min

Catalyst	Conversion (%)	Selectivity (%)	
		Knoevenagel product	Other products
SiO_2	61.1	95.4	4.6
Li/SiO_2	45.1	82.7	17.3
Na/SiO_2	49.2	91.5	8.5
K/SiO_2	78.6	95.3	4.7
Rb/SiO_2	51.9	95.2	4.8
Cs/SiO_2	47.9	95.9	4.1
Al_2O_3	45.5	74.8	25.2
Li/Al_2O_3	59.0	83.3	16.7
Na/Al_2O_3	63.5	82.7	17.3
K/Al_2O_3	90.0	89.8	10.2
Rb/Al_2O_3	63.2	82.1	17.9
Cs/Al_2O_3	73.1	87.2	12.8
$Nb_2O_5 \cdot nH_2O$	57.7	82.6	17.4
Li/$Nb_2O_5 \cdot nH_2O$	50.9	87.9	12.1
Na/$Nb_2O_5 \cdot nH_2O$	52.3	93.0	7.0
K/$Nb_2O_5 \cdot nH_2O$	63.9	93.0	7.0
Rb/$Nb_2O_5 \cdot nH_2O$	60.3	86.8	13.2
Cs/$Nb_2O_5 \cdot nH_2O$	38.1	92.4	7.6
Nb_2O_5	29.3	91.5	8.5
Li/Nb_2O_5	42.8	70.0	30.0
Na/Nb_2O_5	55.4	95.6	4.4
K/Nb_2O_5	59.4	94.6	5.4
Rb/Nb_2O_5	65.6	92.9	7.1
Cs/Nb_2O_5	35.7	93.1	6.9

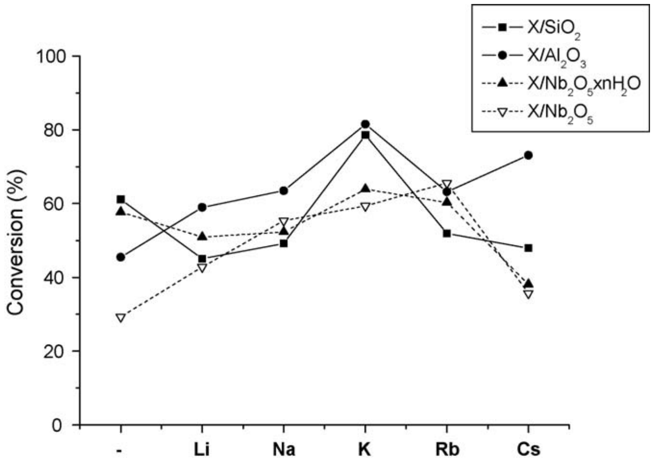
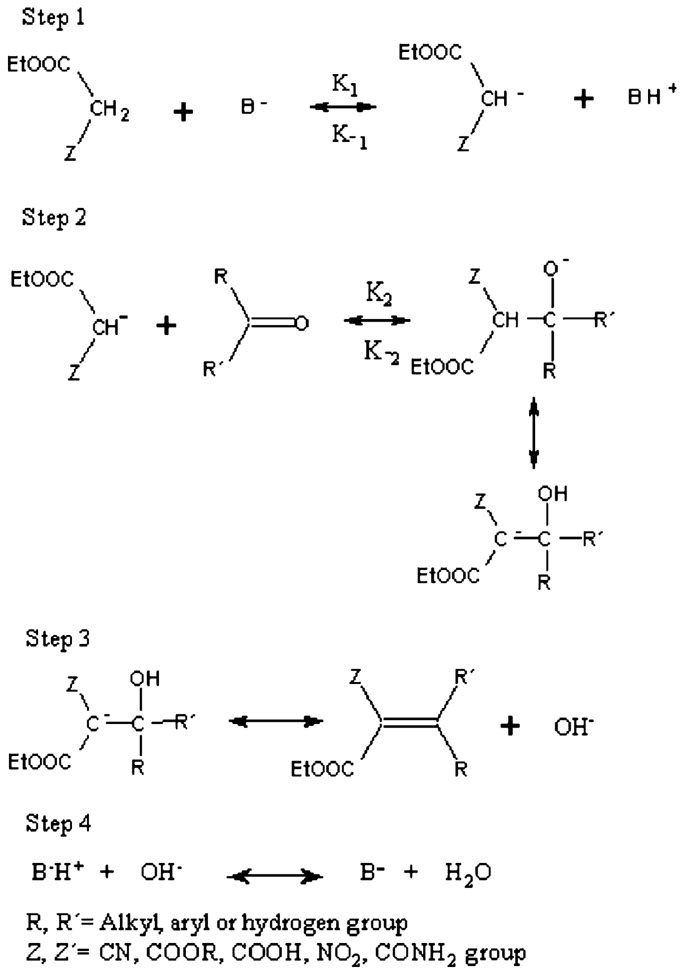


Fig. 2. Influence of the nature of alkali metals located in different materials (SiO_2/X, Al_2O_3/X, $Nb_2O_5 \cdot nH_2O$/X and Nb_2O_5/X (X = Li, Na, K, Rb, Cs)) in the condensation of benzaldehyde with ethyl acetoacetate ($pK_a = 10.7$) at 413 K during 300 min.



Scheme 2. Reaction mechanism of Knoevenagel condensation (R,Ŕ = alkyl, aryl or hydrogen group, Z,Ź = CN, COOR, NO_2, $CONH_2$ group).

To estimate the kinetic rate constants for all the catalysts, the following reaction model has been assumed (Scheme 2).

In the first step, the catalyst abstracts a proton from the methylenic compound, forming a stabilized carbanion. The carbanion, in a second step, attacks the carbonyl group of the benzaldehyde, forming a C–C bond and the corresponding adduct. Finally, in the third step, the adduct so formed, by elimination of the hydroxyl group as hydroxide ion, affords the Knoevenagel condensation product. In a forth step, water is generated and the active sites of the catalyst are restored.

Considering a kinetic expression of second order [14] that is, the controlling step is the nucleophilic attack of the carbanion on the carbonyl group of the benzaldehyde (step 2):

$$r = k[\text{methylenic compound}][\text{benzaldehyde}]$$

where r is the reaction rate and k is the constant rate. Since the concentration of the methylenic compound and benzaldehyde are the same, the integrated rate equation is

$$\frac{1}{A_0(1-x)} = k(t) + \frac{1}{[A_0]}$$

where A_0 is the starting concentration of the reactant, x is the conversion of the product and t is the reaction time.

The results shown in Tables 2–3 were obtained by fitting this model for the condensation of benzaldehyde with ethyl cyanoacetate and diethyl malonate.

Table 2
Kinetic rate constants for the condensation of benzaldehyde (14 mmol) and ethyl cyanoacetate (14 mmol) using 0.031 g of catalyst at 413 K

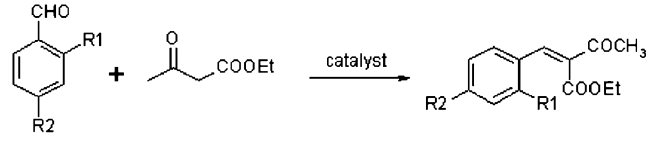
Cation	k ($\times 10^{-5}$ M^{-1} s^{-1} m^{-2})			
	SiO_2	Al_2O_3	$Nb_2O_5{\cdot}nH_2O$	Nb_2O_5
–	0.1	0.3	6.5	5.8
Li	4.0	0.4	63.0	26.1
Na	10.8	5.0	13.3	6.7
K	23.3	9.9	1.4	3.3
Rb	47.6	14.5	2.7	2.2
Cs	45.7	17.0	1.0	2.7

Concerning the role of the support nature (SiO_2, Al_2O_3, Nb_2O_5 (hydrated and dehydrated)) in the sequence of the activity one should consider the alkali metal–support interaction (MSI) and the strength of proton hold by basic sites. The latter is determined by the strength of basic sites depending on the support nature (metal–support interaction). Therefore, niobia supports well known as SMSI (strong metal–support interacted) matrices [13] leads to the different activity sequence if compare with those for silica- and alumina-modified samples. Both niobia pristine materials seem to be modified during the Knoevenagel reaction towards the achievement of high activity after ~100 min of the reaction time for $pK_a = 9$. This activity diminishes by the modification with alkali metals. It is not a case of the reaction required the higher strength of basicity ($pK_a = 10.7$). Taking into account the presented reaction steps (Scheme 2) it is clear that proton has to be abstracted from basic centres in the last step (step 4). Therefore, too strong interaction between basic centers B^- and H^+ causes the decrease of the reaction rate (Table 2). On the other hand too weak interaction makes the first step slower. Importantly, this interaction is influenced by metal–support interaction, i.e. by the support nature. The above consideration explains the nonlinear relationship between the nature of the alkali metal and the activity. In this view it is reasonable the highest activity of potassium-doped silica and rubidium-modified niobia (Fig. 2).

From these results (Fig. 1 and Tables 1–2) it is clear that most of basic sites present in the unmodified supports (SiO_2, Al_2O_3, $Nb_2O_5{\cdot}nH_2O$ and Nb_2O_5) are able to abstract protons of $9 \le pK_a \le 10.7$ and a large number of sites are able to abstract protons of $10.7 \le pK_a \le 13.3$. When the pristine supports are modified by impregnation with the alkali metals it is observed an increase of basicity for silica and alumina supports whereas for the alkali modified hydrated and dehydrated niobia it is observed a decrease of basicity. The kinetic data shown in Tables 2 and 3 indicate that for the reaction involving $pK_a = 9$ the k value increases from Li to Cs on silica and alumina, whereas it decreases in the same order on niobia-based catalysts. Interestingly, for the condensation of benzaldehyde and diethyl malonate ($pK_a = 13.3$) the k values on niobia-supported catalysts are much higher than on the others. That shows the role of strong niobia–alkali metal

Table 3
Kinetic rate constants for the condensation of benzaldehyde (7 mmol) and diethyl malonate (7 mmol) using 0.190 g of catalyst at 403 K

Cation	k ($\times 10^{-8}$ M^{-1} s^{-1} $m^{-2}{}_{cat}$)			
	SiO_2	Al_2O_3	$Nb_2O_5{\cdot}nH_2O$	Nb_2O_5
–	0.6	2.0	9.8	3.5
Li	1.2	9.7	23.7	7.9
Na	1.3	2.9	9.3	7.2
K	8.9	1.8	14.0	5.4
Rb	3.4	2.5	7.6	8.9
Cs	2.7	0.8	6.8	11.3



1 (a-c)

A (a-c)

	R_1	R_2
Benzaldehyde (1a)	H	H
2-nitrobenzaldehyde (1b)	NO_2	H
4-nitrobenzaldehyde (1c)	H	NO_2

Scheme 3. Knoevenagel condensation of a series of substituted benzandehydes **1** (**a**–**c**) with ethylacetoacetate using K/SiO_2 and K/Al_2O_3 as catalysts. Synthesis of intermediates **A** (**a**–**c**) for the production of 1,4-dihydropyridines.

Table 4
Yields obtained in the reaction of substituted benzaldehydes (2-nitrobenzaldehyde and 4-nitrobenzaldehyde) with ethyl acetoacetate at 433 K

Catalyst	T (K)	R_1	R_2	Yield (%)
K/SiO_2	413	H	H	74.9
	433	NO_2	H	40.0
	433	H	NO_2	31.5
K/Al_2O_3	413	H	H	80.8
	433	NO_2	H	30.4
	433	H	NO_2	43.4

Reaction time: 5 h.

species interaction that enhances the strength of basic centers on the catalyst surface.

3.3. Preparation of calcium antagonist intermediates

As mentioned above, Knoevenagel condensation is used to prepare fine chemical intermediates. The condensation of a series of substituted benzaldehydes **1** (**a**–**c**) with ethyl acetoacetate using all these series of catalysts were carried out for the preparation of 1,4-dihydropyridine intermediates (A) (Scheme 3). Some 1,4-dihydropiridines (nifendipine, nitrendipine, nicardipine) are used for different therapeutic uses such as antihypertensives and calcium channel blockers [10–15]. The potassium-modified silica and alumina samples were the most active catalysts in the condensation of benzaldehyde with ethyl acetoacetate (Fig. 2) so we shown in a representative way the results belonged to these catalysts.

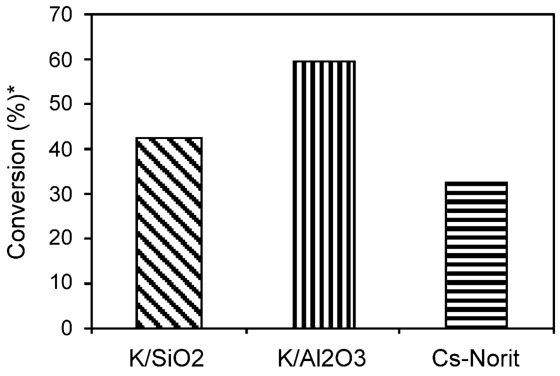


Fig. 3. Effect of the type of catalyst (2%) used in the condensation of benzaldehyde with ethyl acetoacetate at 413 K. Comparison between alkali metal-modified oxide supports catalysts (K/SiO_2 and K/Al_2O_3) and an alkali activated carbon catalyst (Cs-Norit). *Time reaction = 180 min.

The reactions were carried out at 433 K. The results obtained for the condensation of ethyl acetoacetate with benzaldehyde derivatives are given in Table 4. The catalyst K/SiO_2 was the most active catalyst when the substituted benzaldehyde was 2-nitrobenzaldehyde and K/Al_2O_3 was the best in the case of 4-nitrobenzaldehyde. The activity of the catalysts in the reaction of the unsubstituted benzaldehyde and ethyl acetoacetate at 413 K for 180 min were compared with the activity obtained using another solid basic catalyst in this case an alkali activated carbon, Cs-Norit (Fig. 3) [14]. The trend of the activity found was: $K/Al_2O_3 > K/SiO_2 >$ Cs-Norit.

4. Conclusions

The silica, alumina and niobia (hydrated and dehydrated) matrices exhibit basic properties, showing most of theirs basic sites able to abstract protons of $9 \leq pK_a \leq 10.7$ and few of them able to abstract protons with $10.7 \leq pK_a \leq 13.3$. The modification of silica and alumina supports with alkali metal species leads to a significantly increase of basicity in the range $9 \leq pK_a \leq 10.7$ and a little in the range $10.7 \leq pK_a \leq 13.3$. On the other hand the modification of niobia (hydrated and dehydrated) supports, giving rise to strong alkali metal–support interaction, causes the diminishing of existing basic sites in the range $9 \leq pK_a \leq 10.7$, but these catalysts show enough basicity for the abstraction of protons in the range $10.7 \leq pK_a \leq 13.3$.

The Knoevenagel condensation has also been used in the preparation of some intermediates compounds for the synthesis of 1,4-dihydropyridines. This method is presented as a clean and green method to prepare these compounds in liquid phase using alkali metal oxides as catalysts in the absence of any solvent. Thus, K/SiO_2 and K/Al_2O_3 are active and selective catalysts in this synthesis by condensation of benzaldehyde and different substituted benzaldehydes with ethyl acetoacetate. Moreover, K/SiO_2 and K/Al_2O_3 showed more activity in this reaction than others solid basic catalysts as an alkali activated carbon, Cs-Norit.

The use of alkali metal oxides can be extended for the preparation of intermediates in the manufacturing of dihydropyridines. The application of solid bases of these types introduces advantages for industrial manufacturers, in the separation and regeneration of the catalyst and an easier work-up and purification of products.

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