

# Study on dry-media microwave azalactone synthesis on different supported KF catalysts: influence of textural and acid–base properties of supports

2 PERKIN

Felipa M. Bautista, Juan M. Campelo, Angel García, Diego Luna,\* José M. Marinas and Antonio A. Romero

Departamento de Química Orgánica, Facultad de Ciencias, Universidad de Córdoba, Campus Universitario de Rabanales, Edificio C-3, E-14014 Córdoba, Spain. E-mail: qo1lumad@uco.es

Received (in Cambridge, UK) 16th October 2001, Accepted 28th November 2001

First published as an Advance Article on the web 10th January 2002

Twenty-five inorganic solids studied as supports for KF were screened with respect to the synthesis of the azalactone obtained by dry-media condensation of *p*-hydroxybenzaldehyde with hippuric acid in acetic anhydride (1 : 1 : 4, molar ratio), in 3 g of 10 wt% KF support catalysts. The results obtained indicate that there was a number of supported KF catalysts with conversions higher than or comparable to that obtained by the classical Erlenmeyer method of azalactone synthesis. Furthermore, not only were there very important differences in the catalytic behavior of different KF support systems, but also these differences are closely related to the procedure used in the reaction heating. In this respect, the well-documented KF–Al<sub>2</sub>O<sub>3</sub> was the best catalyst when reactions were conducted under conventional heating. However, when reactions were carried out in a domestic microwave oven, KF supported on AlPO<sub>4</sub>, TiO<sub>2</sub> or Zn<sub>3</sub>(PO<sub>4</sub>)<sub>2</sub> were better catalysts than KF–Al<sub>2</sub>O<sub>3</sub>. The importance of the textural and acid–base properties of solid inorganic supports was also demonstrated with respect to the catalytic behavior of supported KF catalysts. Finally, results obtained in the synthesis of thirteen different azalactones, lead us strongly to recommend the procedure using microwave irradiation and KF–AlPO<sub>4</sub>, over classical heating with KF–Al<sub>2</sub>O<sub>3</sub>. The advantages are good yields, easier work-up, a significant decrease in reaction times, and easy re-use of catalysts when operated in dry-media, especially by use of a domestic microwave oven.

## Introduction

Azalactones, or 2,4-substituted oxazolin-5-ones, are important intermediates in the preparation of several fine chemicals, including amino acids,<sup>1</sup> peptides,<sup>2</sup> antimicrobial or antitumor compounds,<sup>3</sup> some heterocycle precursors<sup>4</sup> as well as biosensors or coupling and/or photosensitive composition devices for proteins.<sup>5</sup> They are usually obtained by condensation reactions of different arylaldehydes with hippuric acid in acetic anhydride, in the presence of anhydrous sodium acetate as a homogeneous basic catalyst, according to the Erlenmeyer method.<sup>6</sup> This classical method has generally been shown to produce *Z*-stereoisomers, although several procedures have reportedly obtained the corresponding *E*-stereoisomers.<sup>7</sup> Furthermore, Pb(OAc)<sub>2</sub> is used when the reaction is extended to  $\alpha$ -hydroxyketones,  $\alpha,\alpha'$ -dihydroxyketones,  $\alpha$ -diketones and methylcyclohexanones.<sup>3b,8</sup> Recently, an improved procedure has been reported for the synthesis of arylideneoxazolones from hippuric acid and aromatic aldehydes in the presence of acetic anhydride and anhydrous zinc chloride<sup>9</sup> as well as by using microwave irradiation.<sup>10</sup>

The use of environmentally friendly inorganic solids, as catalysts or reaction media, is rapidly increasing<sup>11</sup> because these reactions, compared to their homogeneous counterparts, often involve milder experimental conditions, an easier set-up and work-up, more rapid reaction rates, increased yield and/or selectivity, easy removal, recycling and reuse of catalysts, and minimal wastes. Thus, we have studied the use of the amorphous solids AlPO<sub>4</sub> and AlPO<sub>4</sub>–Al<sub>2</sub>O<sub>3</sub> as catalysts for Diels–Alder reactions,<sup>12</sup> 1,3-dioxolane synthesis by acetalization of different carbonyl compounds,<sup>13</sup> tetrahydropyranlation of alcohols and phenols,<sup>14</sup> the liquid-phase retro-aldolization of diacetone alcohol<sup>15</sup> as well as for Knoevenagel condensations in dry media.<sup>16</sup> These solids have also been used as catalysts in a

number of gas-phase organocationic reactions,<sup>17</sup> as metal supports in the liquid-phase hydrogenation of alkenes and alkynes bearing a variety of organic functional groups,<sup>18</sup> as a KMnO<sub>4</sub> support in the benzaldehyde oxidation reaction,<sup>19</sup> and as a KF support in the Michael addition of nitromethane to but-3-en-2-one.<sup>20</sup>

The classical Erlenmeyer synthesis of azalactones consists of a condensation reaction between a carbonyl group and the acidic methylene of hippuric acid (or acetylglycine), with the loss of a water molecule, which works well with aromatic aldehydes, moderately well with ketones, but often fails with hindered or less active ketones. Thus, in principle, it is a condensation reaction very similar to that of Knoevenagel, Michael or Aldol condensations, which can be effected by many reagents including KF–Al<sub>2</sub>O<sub>3</sub> catalysts in dry-media under conventional heating,<sup>11a,c,21</sup> as well as under microwave irradiation.<sup>22</sup> In fact, any condensation reaction where water or alcohol are eliminated were found to constitute good candidates for microwave treatment, and in like manner, reactions like these that produce water are very sensitive to the catalytic action of KF–Al<sub>2</sub>O<sub>3</sub> catalysts.<sup>23</sup>

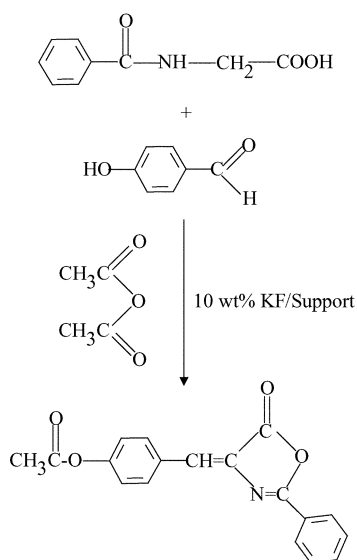
Thus, KF–Al<sub>2</sub>O<sub>3</sub> is among the best studied and most frequently employed supported reagents although the reasons for its high catalytic activity remain a point of contention.<sup>23</sup> The influence of different alkali-metal fluorides<sup>24</sup> was investigated very early on even though there is still not much information about the effects of different supports at the present time.<sup>25</sup> In this respect, we had previously found that KF–ZnO was a better catalyst than KF–Al<sub>2</sub>O<sub>3</sub> in a Michael condensation reaction carried out in dry-media conditions.<sup>20</sup>

Thus, in the present study we have undertaken a screening of different inorganic solids as supports for KF in azalactone synthesis, through the dry-media condensation of arylaldehydes

with hippuric acid in acetic anhydride, under conventional heating, and under microwave irradiation in a domestic microwave oven, at atmospheric pressure through use of an open reaction vessel. Furthermore, the influence of textural and acid–base properties of supports on the catalytic behavior of the supported KF catalyst was also investigated because, under dry-media reaction conditions, the textural and acid–base properties of solid surfaces must play a similar role to that of the solvent in homogeneous processes.

## Results and discussion

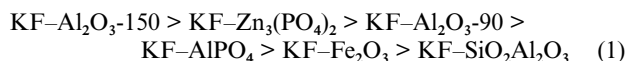
The screening of twenty-five different inorganic solids studied as supports for KF was carried out with respect to the synthesis of the azalactone obtained by the dry-media condensation of *p*-hydroxybenzaldehyde with hippuric acid in acetic anhydride (1 : 1 : 4, molar ratio), with 3 g of 10 wt% KF support catalysts. As outlined in Scheme 1, and according to the literature,<sup>6c</sup> the



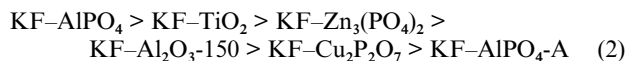
Scheme 1

hydroxy group is acetylated at the same time as the condensation reaction is carried out.

The results collected in Table 1 indicate that, not only is there a very pronounced influence of the support on the catalytic behavior of supported KF catalysts, but also that these differences are closely related to the activation procedure. Thus, when the reaction was conducted under conventional heating, the best results were obtained according to the following sequence



with yields ranging between 72.5% and 39.8%. However, when reactions were carried out with a domestic microwave oven, the sequence was as follows



now with yields ranging between 86.8% and 37.1%.

Furthermore, there was a number of supported KF catalysts with conversions higher, or comparable, to that obtained by the Erlenmeyer method. Thus, additional experiments were carried out to gain further insight into the nature of the active basic sites of KF–Al<sub>2</sub>O<sub>3</sub>-150, which is the best catalyst under conventional heating. The same reaction was carried out with NaOAc, under the conditions of the classical Erlenmeyer pro-

cedure,<sup>6</sup> as well as with the same amount of NaOAc supported on Al<sub>2</sub>O<sub>3</sub>-150, Table 2. Taking into account that the classical Erlenmeyer procedure gave 69.1% yield and that the yield obtained with a NaOAc–Al<sub>2</sub>O<sub>3</sub>-150 catalyst was 55.5% under conventional heating, and 21.3%, when the microwave oven was used, we can conclude that KF–NaOAc is a better catalyst than NaOAc alone, and than Al<sub>2</sub>O<sub>3</sub> alone or with NaOAc, for azalactone synthesis. In this respect, when we try to effect azalactone synthesis under microwave irradiation in homogeneous conditions (with NaOAc and without support) only a 2.4% yield was obtained.

The apparent contradiction with the literature where high yields are obtained,<sup>10</sup> is solved by taking into account that such reactions, as compared to the present experimental conditions, were carried out with a much greater amount of Ac<sub>2</sub>O (four times as much). Thus, Ac<sub>2</sub>O also plays the role of solvent, which provides the driving force of the condensation reaction due to its high boiling point (139 °C). In fact, when carried out in this way, a large quantity of Ac<sub>2</sub>O evaporated, so it was necessary to work with a large amount of “Ac<sub>2</sub>O solvent” to obtain the yields indicated.<sup>10</sup>

At the present time the catalytically active basic sites in KF–Al<sub>2</sub>O<sub>3</sub> are associated with several reaction products of KF and some surface atoms on the Al<sub>2</sub>O<sub>3</sub> support.<sup>23</sup> Thus, instead of the support being the true catalyst, the interaction of several support surface species and KF can give rise to basic sites, which differ not only in nature, but also in number and strength, and these may in fact act as the true catalysts. Consequently, in order to determine the role of the surface properties of inorganic solids on the catalytic behavior of supported KF solids, we measured their surface areas (BET method)<sup>12–20</sup> as well as their acid–base properties (determined by a spectrophotometric method using pyridine and benzoic acid as titrant agents),<sup>12–20</sup> Table 3. Furthermore, we developed a correlation matrix by using all the data in Table 1 and Table 3. The values of the slopes and intercepts obtained in the regression analysis of well-correlated parameter pairs are collected in Table 4, where the corresponding significance levels are also indicated.

Results obtained indicate that textural and acid–base properties of the support play an important role in the catalytic behavior of 10 wt% supported KF catalyst but, at the same time, these effects are not always exactly the same depending on the heating procedure. This is in contrast with the good correlation between *Y*<sub>MW</sub> and *Y*<sub>CLAS</sub> (the azalactone yields obtained by microwave irradiation and by classical heating), which could be interpreted as the standard of the support effects for both kinds of reaction. However, when we consider the good correlations obtained between the azalactone yield by classical heating, *Y*<sub>CLAS</sub>, and the inverse of the number of acid sites titrated with pyridine, 1/*X*<sub>m</sub>A, the negative influence of the acidity of the inorganic solid used as the KF support is obvious. At the same time, for reactions conducted under microwave irradiation, the specific basicity of the support (or number of basic sites titrated by benzoic acid per unit surface area) *X*<sub>m</sub>B/*S*<sub>BET</sub>, is that which basically determines the *Y*<sub>MW</sub> values.

In summary, we plainly see that the support should preferably not have acid sites for conventional heating, while good yields are obtained for reactions conducted under microwave heating when the number of basic sites is as high as possible for a given surface area, *S*<sub>BET</sub>. Both requirements are usually related, but they are not exactly the same, as can be seen in Table 3. These results could indicate that, depending on the type of heating used (classical or microwave), different basic surface-active sites take part in the condensation reaction. In the literature,<sup>23a</sup> the existence of a heterogeneity of active sites it is considered for KF–Al<sub>2</sub>O<sub>3</sub>, not only in nature (F<sup>−</sup>, AlF<sub>4</sub><sup>−</sup>, AlF<sub>6</sub><sup>3−</sup>, OH<sup>−</sup>, O<sup>2−</sup> and CO<sub>3</sub><sup>2−</sup>), but also in their strength, which will depend on the relative concentration of the KF and on some aspects related to the synthetic procedure, such as time

**Table 1** Isolated weights and yields obtained with different 10 wt% supported KF catalysts in the synthesis of 4-(4'-acetoxybenzylidene)-2-phenyloxazol-5(4*H*)-one, under classical heating as well as by microwave irradiation under standard conditions, 15 minutes at 450 W

Support	Classical heating		Microwave irradiation	
	Isolated weight/g	Yield (%)	Isolated weight/g	Yield (%)
Al <sub>2</sub> O <sub>3</sub> -90	0.711	46.3	0.474	30.9
Al <sub>2</sub> O <sub>3</sub> -150	1.113	72.5	0.983	51.2
ZnO	0.543	35.4	0.493 <sup>a</sup>	32.2 <sup>a</sup>
Fe <sub>2</sub> O <sub>3</sub>	0.679	44.2	0.537 <sup>b</sup>	35.0 <sup>a</sup>
Sepiolite	0.361	23.5	0.183	11.9
SiO <sub>2</sub>	0.326	21.2	0.019	1.2
3SiO <sub>2</sub> Al <sub>2</sub> O <sub>3</sub>	0.611	39.8	0.396	25.8
TiO <sub>2</sub>	0.547	33.8	0.942 <sup>a</sup>	61.3 <sup>a</sup>
Carbon	0.399	26.0	0.000 <sup>b</sup>	0.0 <sup>b</sup>
CuCrO <sub>4</sub> ·2CuO·2H <sub>2</sub> O	0.000	0.0	0.000	0.0
AlPO <sub>4</sub> ·H <sub>2</sub> O	0.693	45.2	1.332	86.8
AlPO <sub>4</sub> -A	0.177	11.5	0.570	37.1
Ca <sub>2</sub> (PO <sub>4</sub> ) <sub>2</sub>	0.104	6.8	0.031	2.0
FePO <sub>4</sub> · <i>n</i> H <sub>2</sub> O	0.230	15.0	0.059	3.2
Zn <sub>3</sub> (PO <sub>4</sub> ) <sub>2</sub> ·4H <sub>2</sub> O	0.912	59.4	0.849 <sup>a</sup>	55.3 <sup>a</sup>
Cu <sub>3</sub> P <sub>2</sub> O <sub>7</sub> · <i>n</i> H <sub>2</sub> O	0.396	25.0	0.610	39.4
Al <sub>2</sub> (SO <sub>4</sub> ) <sub>3</sub> ·18H <sub>2</sub> O	0.000	0.0	0.000	0.0
CaSO <sub>4</sub> ·2H <sub>2</sub> O	0.246	16.0	0.393	25.6
Cr <sub>2</sub> (SO <sub>4</sub> ) <sub>3</sub> · <i>n</i> H <sub>2</sub> O	0.224	14.6	0.360	23.4
MnSO <sub>4</sub>	0.000	0.0	0.000	0.0
Fe <sub>2</sub> (SO <sub>4</sub> ) <sub>3</sub> ·9H <sub>2</sub> O	0.151	9.8	0.546	35.6
CoSO <sub>4</sub> ·7H <sub>2</sub> O	0.208	13.6	0.000	0.0
NiSO <sub>4</sub> ·6H <sub>2</sub> O	0.061	4.0	0.120	7.8
CuSO <sub>4</sub>	0.473	30.8	0.083	5.4
ZnSO <sub>4</sub> ·7H <sub>2</sub> O	0.000	0.0	0.000	0.0

<sup>a</sup> It was irradiated for 15 minutes at only 150 W. <sup>b</sup> It burned before two minutes, at only 150 W.

**Table 2** Isolated weights and yields obtained with NaOAc catalysts, unsupported under classical Erlenmeyer experimental conditions, and supported on Al<sub>2</sub>O<sub>3</sub>, in the synthesis of 4-(4'-acetoxybenzylidene)-2-phenyloxazol-5(4*H*)-one, with classical heating as well as by microwave irradiation

Catalyst	Classical heating		Microwave irradiation	
	Isolated weight/g	Yield (%)	Isolated weight/g	Yield (%)
NaOAc	1.060 <sup>a</sup>	69.1 <sup>a</sup>	0.037	2.4
NaOAc-Al <sub>2</sub> O <sub>3</sub> -150	0.852	55.5	0.327	21.3

<sup>a</sup> Erlenmeyer conditions, 4 h under reflux.

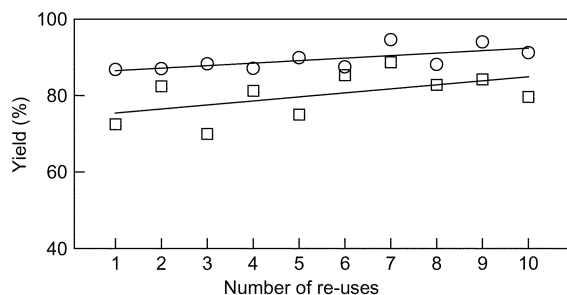
**Table 3** Surface area (*S*<sub>BET</sub>) and acid–base properties of different inorganic solids used as 10 wt% KF catalyst support

Support	<i>S</i> <sub>BET</sub> /m <sup>2</sup> g <sup>-1</sup>	Acidity vs. pyridine ( <i>X</i> <sub>m</sub> A)/μmol g <sup>-1</sup>	Basicity vs. benzoic acid ( <i>X</i> <sub>m</sub> B)/μmol g <sup>-1</sup>
Al <sub>2</sub> O <sub>3</sub> -90	65.7	4.9	357.5
Al <sub>2</sub> O <sub>3</sub> -150	45.3	9.3	289.6
ZnO	4.0	0.4	2.0
Fe <sub>2</sub> O <sub>3</sub>	2.5	0.4	3.7
Sepiolite	96.9	31.0	174.0
SiO <sub>2</sub>	344.2	206.0	164.0
3SiO <sub>2</sub> Al <sub>2</sub> O <sub>3</sub>	7.4	2.1	271.5
TiO <sub>2</sub>	8.0	0.9	5.3
Carbon	743.0	124.0	132.0
CuCrO <sub>4</sub> ·2CuO·2H <sub>2</sub> O	4.9	4.5	20.6
AlPO <sub>4</sub> ·H <sub>2</sub> O	19.6	42.3	104.0
AlPO <sub>4</sub> -A	173.9	212.1	297.9
Ca <sub>2</sub> (PO <sub>4</sub> ) <sub>2</sub>	37.6	2.7	48.5
FePO <sub>4</sub> · <i>n</i> H <sub>2</sub> O	11.7	25.4	8.9
Zn <sub>3</sub> (PO <sub>4</sub> ) <sub>2</sub> ·4H <sub>2</sub> O	< 0.1	0.1	1.6
Cu <sub>3</sub> P <sub>2</sub> O <sub>7</sub> · <i>n</i> H <sub>2</sub> O	< 0.1	13.8	9.0
Al <sub>2</sub> (SO <sub>4</sub> ) <sub>3</sub> ·18H <sub>2</sub> O	13.4	37.8	6.1
CaSO <sub>4</sub> ·2H <sub>2</sub> O	5.3	1.6	20.0
Cr <sub>2</sub> (SO <sub>4</sub> ) <sub>3</sub> · <i>n</i> H <sub>2</sub> O	0.2	0.4	0.3
MnSO <sub>4</sub>	< 0.1	0.4	0.5
Fe <sub>2</sub> (SO <sub>4</sub> ) <sub>3</sub> ·9H <sub>2</sub> O	< 0.1	67.2	0.3
CoSO <sub>4</sub> ·7H <sub>2</sub> O	< 0.1	11.5	12.8
NiSO <sub>4</sub> ·6H <sub>2</sub> O	9.4	12.2	21.4
CuSO <sub>4</sub>	< 0.1	14.5	1.1
ZnSO <sub>4</sub> ·7H <sub>2</sub> O	1.6	12.4	3.8

and calcination temperature. When different supports are used, the heterogeneity of surface active sites must increase in new basic surface species and also in different strengths. Microwave irradiation would probably depend on the total number of basic active sites, but classical heating could be more dependent on basic surface active sites of a certain strength, best obtained in KF–Al<sub>2</sub>O<sub>3</sub> through a co-operative action of F<sup>-</sup> on the Al<sub>2</sub>O<sub>3</sub> surface.<sup>23c</sup>

With respect to the favorable results obtained with AlPO<sub>4</sub> as a KF support for reactions carried out under microwave activation, the possible use of this material as a microwave substrate was proposed some years ago<sup>26</sup> because it is completely isostructural with silica, exhibiting the same polymorphic transformations. However, for the moment these are the first results presented in this respect.

Finally, in accordance with the results in Fig. 1 and Table 5,



**Fig. 1** Reusability of KF–AlPO<sub>4</sub> (○) under microwave irradiation and KF–Al<sub>2</sub>O<sub>3</sub> (□) under classical heating, in the synthesis of 4-(4'-acetoxybenzylidene)-2-phenyloxazol-5(4*H*)-one under standard conditions.

we can confirm the general application of supported KF as a basic catalyst for azalactone synthesis in dry-media, under

**Table 4** Results for the single regression models ( $y = ax + b$ ) between some surface properties of 10 wt% supported KF catalysts, in Table 1, and the isolated yields (in %) under classical heating ( $Y_{\text{CLAS}}$ ) and microwave irradiation ( $Y_{\text{MW}}$ ), in Table 2, as well as the corresponding significance levels

$Y$	$x$	$a$	$b$	Significance (%)
$X_{\text{m}}A$	$X_{\text{m}}B$	0.26	17.73	95.0
$X_{\text{m}}A$	$S_{\text{BET}}$	0.24	19.65	99.8
$Y_{\text{CLAS}}$	$1/X_{\text{m}}A$	2.47	20.07	99.5
$Y_{\text{MW}}$	$Y_{\text{CLAS}}$	0.64	10.27	96.8
$Y_{\text{MW}}$	$X_{\text{m}}B/S_{\text{BET}}$	4.25	17.30	91.9

**Table 5** Isolated yields obtained in the synthesis of different 4-ylidene-2-phenyloxazol-5(4*H*)-ones, with 10 wt% KF–AlPO<sub>4</sub> under microwave irradiation, with 10 wt% KF–Al<sub>2</sub>O<sub>3</sub> under classical heating, and with CH<sub>3</sub>CO<sub>2</sub>Na by the standard Erlenmeyer synthesis procedure. References in the literature are also included

Entry	Azalactone (4-ylidene-2-phenyloxazol-5(4 <i>H</i> )-one)	Isolated yields (%)			
		KF–AlPO <sub>4</sub>	KF–Al <sub>2</sub> O <sub>3</sub>	NaOAc <sup>a</sup>	References
1	4-Benzylidene-	74.1	81.2	84.0	70–90 <sup>6c-g,7a,b,10</sup>
2	4-(4'-Acetoxybenzylidene)-	86.8	72.5	69.1	80–85 <sup>6c,d,7b</sup>
3	4-(2'-Acetoxybenzylidene)-	45.0	57.0	47.8	18 <sup>6c,d,7b</sup>
4	4-(4'-Methylbenzylidene)-	73.2	75.1	78.6	70–80 <sup>6c,e,7b,10</sup>
5	4-(2'-Methylbenzylidene)-	48.4	70.3	58.2	40 <sup>6f</sup>
6	4-(4'-Nitrobenzylidene)-	53.0	72.6	55.2	60 <sup>6c-e,7b</sup>
7	4-(4'-Chlorobenzylidene)-	55.1	66.2	62.7	70–79 <sup>6c-g,7b,10</sup>
8	4-(4'-Methoxybenzylidene)-	76.6	74.4	68.6	63–80 <sup>6c-g,7b,10</sup>
9	4-(3',4'-Methylenedioxybenzylidene)-	70.0	81.4	72.6	70–80 <sup>6c,g,7b</sup>
10	4-(3'-Phenylpropenylidene)-	64.6	72.8	73.8	10–75 <sup>6c,d,7a</sup>
11	4-(1'-Methyl-3'-phenylpropenylidene)-	44.0	65.0	49.8	
12	4-(But-2'-enylidene)-	33.2	38.8	40.1	
13	4-Cyclohexylidene-	14.5	20.5	19.0	19.0 <sup>1a</sup>

<sup>a</sup> Erlenmeyer synthesis conditions,<sup>6</sup> 4 h under reflux.

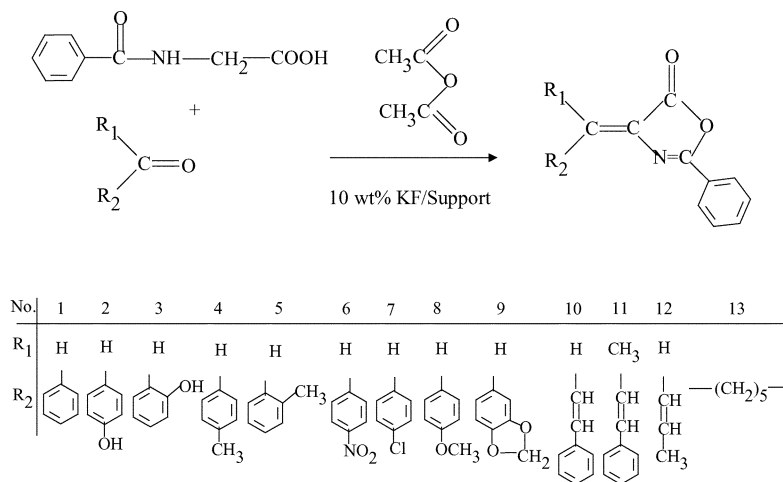
conventional heating as well as by microwave irradiation. Thus, we have selected the two best catalysts, KF–Al<sub>2</sub>O<sub>3</sub>-150 for conventional heating and KF–AlPO<sub>4</sub> for microwave irradiation, to carry out a study on their stability over repeated use, and in the condensation of several different carbonyl compounds and hippuric acid, in order to synthesize different azalactones (Scheme 2). From the results shown in Fig. 1 it is easy to confirm the high operational stability of the catalysts studied because after ten consecutive reactions, in the synthesis of 4-(4'-acetoxybenzylidene)-2-phenyloxazol-5(4*H*)-one under standard conditions, the catalytic activity of both supported KF catalysts is clearly maintained.

The yields obtained in the synthesis of different azalactones in dry-media are comparable to those obtained by classical Erlenmeyer synthesis as well as to those in the literature. Classical Erlenmeyer synthesis affords generally the *Z*-derivatives.<sup>7b</sup> Here the presence of *E* isomers was excluded by TLC: the reaction products were always exactly the same, independent of the reaction procedure, classical or dry-media. However, these results also indicate that thermal activation is probably the driving force in the microwave experiments, taking into account that after microwave irradiation the reaction is accompanied by a significant increase in temperature. These temperatures cannot easily be determined in the domestic microwave oven used, however, values higher than 130 °C were obtained when they were measured approximately.

In general, we can conclude from the results in Table 5 that the yields obtained with different procedures are similar, so that the most interesting differences are associated with the easier work-up, and the important decrease in reaction time when the reaction is carried out in dry-media, especially when using a domestic microwave oven. The main advantage of heterogeneous catalysis, however, is associated with the possibilities of recovering and reusing the catalysts.

## Conclusions

The experiments described in this research were aimed at extending the use of environmentally friendly inorganic solids to the important classical Erlenmeyer azalactone synthesis. We investigated not only the usual KF–Al<sub>2</sub>O<sub>3</sub> basic catalysts, but also the possibilities of different KF support catalysts, taking into account results previously obtained in the Michael condensation reaction where KF–ZnO was the best catalyst.<sup>20</sup> Furthermore, in the present case we decided also to explore the potential advantages of “MORE” chemistry (microwave-induced organic reaction enhancement),<sup>27</sup> by running the reactions in a domestic microwave oven. Some results obtained



Scheme 2

after the study were expected, such as those which led us to conclude that there were no important differences in yields between reactions carried out according to the classical Erlenmeyer synthesis and under dry-media conditions, with classical heating or microwave irradiation, when the best supported KF catalysts were used. Thus, the easier work-up and the significant decrease in reaction times when dry-media conditions were used, especially with the use of a domestic microwave oven, lead us strongly to recommend this procedure for the synthesis of any type of azalactone.

However, an important and unexpected conclusion obtained was that there were not only very important differences between the KF support catalysts observed during the screening of catalysts, but also that these differences are also closely related to the procedure used in the reaction heating. Thus, after screening we can conclude that, under the present standard experimental conditions the well documented<sup>23–25</sup> Al<sub>2</sub>O<sub>3</sub> was the best support for KF when reactions are conducted under conventional heating. However, this is not true when reactions are carried out in a domestic microwave oven, where AlPO<sub>4</sub>, TiO<sub>2</sub> and Zn<sub>3</sub>(PO<sub>4</sub>)<sub>2</sub> are better supports than Al<sub>2</sub>O<sub>3</sub>-150. What is more, Al<sub>2</sub>O<sub>3</sub> is not the only reasonably good KF support catalyst for condensation reactions. Some inorganic solids, such as phosphates or oxides [such as Zn<sub>3</sub>(PO<sub>4</sub>)<sub>2</sub>, AlPO<sub>4</sub> and Fe<sub>2</sub>O<sub>3</sub>] although not usually employed as supports for reagents, could also easily be used because they are as accessible and inexpensive as Al<sub>2</sub>O<sub>3</sub>. The study of supports other than Al<sub>2</sub>O<sub>3</sub> is even more necessary when microwave oven irradiation is used, because the results clearly indicate that there are some inorganic solids more appropriate for KF supports than Al<sub>2</sub>O<sub>3</sub>.

In this respect, the importance of textural and acid–base properties of solid inorganic supports in the catalytic behavior of supported KF catalysts was also demonstrated. Thus, acidity of supports seems to strongly inhibit the ability of KF support catalysts for reactions under conventional heating. In addition, the specific basicity of supports (number of basic sites/S<sub>BET</sub>) seems to strongly promote the KF catalysts in reactions carried out in a microwave oven. Despite the lack of a more detailed theoretical explanation, these differences could be ascribed to the fact that the participation of KF surface active sites, which take part in the condensation reactions, is not always exactly the same and depends on whether the type of activation used is that of classical heating or microwave.

Finally, according to our results we may conclude that, before directly using the well-documented KF–Al<sub>2</sub>O<sub>3</sub> as the basic catalyst for a condensation reaction under dry-media conditions, it is worthwhile investigating other supported KF systems which might be more active and/or selective, especially if a domestic microwave oven is to be used. For this purpose AlPO<sub>4</sub> should not be overlooked.

## Experimental

### Apparatus

Melting points were determined on a Gallenkamp Mod. MPD-350 apparatus and are uncorrected. Infrared spectra were obtained for KBr pellets on a Bomem, Mod. MB-100 spectrophotometer. <sup>1</sup>H and <sup>13</sup>C NMR spectra were obtained using TMS as an internal standard, on a Bruker AC 400 spectrometer at 400 and 100 MHz, respectively. High-resolution mass spectra were performed on a VG AUTOSPEC (Micromass Instruments) where samples were introduced through a solid probe. Reactions were monitored by thin-layer chromatography (TLC) on Merck silica gel 60 F<sub>254</sub> plates. A conventional domestic microwave oven (Corbero, 700 W max power, equipped with a turntable, timer and five output powers) was used for the microwave-assisted heating reactions.

### Materials

Unless stated otherwise, chemicals were obtained from different commercial sources and used without further purification. Thus, hippuric acid as well as aldehydes and ketones used in the synthesis of different azalactones were purchased from Aldrich Chemical Co. Inorganic solids used as supports for KF were from the following sources: TiO<sub>2</sub> pure anatase was obtained from Aldrich; natural Sepiolite was from Tolsa SA; chromatographic grade SiO<sub>2</sub> (Kieselgel 60), acidic Al<sub>2</sub>O<sub>3</sub>-90 and basic Al<sub>2</sub>O<sub>3</sub>-150 (type T) were from Merck; ZnO, MnSO<sub>4</sub>, Cr<sub>2</sub>(SO<sub>4</sub>)<sub>3</sub>·nH<sub>2</sub>O, Ca<sub>3</sub>(PO<sub>4</sub>)<sub>2</sub>, Al<sub>2</sub>(SO<sub>4</sub>)<sub>3</sub>·18H<sub>2</sub>O and active carbon were from Panreac. All the other inorganic solids listed in Tables 1 and 3 [AlPO<sub>4</sub> H<sub>2</sub>O, Zn<sub>3</sub>(PO<sub>4</sub>)<sub>2</sub>·4H<sub>2</sub>O, and so on], were from Probus. An amorphous AlPO<sub>4</sub> (AlPO<sub>4</sub>-A), obtained according to a sol–gel method previously described,<sup>12–20</sup> was also used as a support. This support was prepared by precipitation from aqueous solutions of AlCl<sub>3</sub>·6H<sub>2</sub>O and H<sub>3</sub>PO<sub>4</sub> (85 wt%) at pH = 6.1 at the “precipitation end point”, with ammonium hydroxide solution. The solid obtained was then washed with isopropyl alcohol and dried at 120 °C for 24 hours.

### Synthesis and characterization of supported KF catalysts

Different inorganic solids were slowly heated in a muffle furnace to reach 400 °C over the course of one hour (100 °C every 15 min). They were then calcined for three hours at this temperature, to remove completely the hydration water before KF impregnation. Surface area, S<sub>BET</sub>, and acid–base properties of the supports summarized in Table 3 were also determined before KF deposition. These were obtained by nitrogen adsorption<sup>12–20</sup> as well as by a spectrophotometric method described elsewhere,<sup>12–20</sup> which allows titration of the amount

of irreversibly adsorbed benzoic acid (BA,  $pK_a = 4.19$ ) or pyridine (PY,  $pK_a = 5.25$ ) employed as titrant agents for basic and acid sites, respectively. The monolayer coverage at equilibrium at 25 °C,  $X_m$  (in  $\mu\text{mol g}^{-1}$ ), was accomplished by applying the Langmuir adsorption isotherm, and is assumed to be a measure of the acidic or basic sites corresponding to the specific  $pK_a$  of the base or acid used in the titration.

Different 10 wt% supported KF catalysts were prepared by impregnation of supports to incipient wetness with (1 : 1) methanol–aqueous solutions of potassium fluoride (Merck, *pa.*).<sup>20</sup> Thus, the slurry obtained by mixing the support, 9 g, and KF solution, 4 ml, (KF, 1 g, MeOH, 2 ml and water, 2 ml) was stirred for 2 hours and then the solvent evaporated off on a rotary vacuum evaporator. Afterwards, the samples were dried at 150 °C in a muffle furnace for 24 h, and then stored in a desiccator. Similarly, for comparative purposes, NaOAc–Al<sub>2</sub>O<sub>3</sub>-150 was prepared by impregnation of anhydrous sodium acetate (0.432 g, 5 mmol) on 3 g of support, but using 4 ml anhydrous MeOH as the solvent.

#### General procedure for the synthesis of 4-ylidene-2-phenyl-oxazol(4H)-5-ones

According to the standard Erlenmeyer procedure,<sup>6</sup> a mixture of hippuric acid (0.896 g, 5 mmol), anhydrous sodium acetate (0.432 g, 5 mmol), acetic anhydride (2 ml, 20 mmol) and the corresponding carbonyl compound, ketone or aldehyde, (5 mmol), was placed in a 25 ml conical flask and heated on an electric hotplate with constant shaking to liquefy the mixture completely. The flask was then heated in a water bath for 4 hours, after which it was cooled to room temperature. Cool water (10 ml) was added, and the mixture was allowed to stand overnight. Crude azalactones were obtained after filtration and washing with aqueous sodium carbonate to remove benzoic acid. The yields indicated in Table 5 correspond to those obtained after recrystallization from acetone–water (2 : 1).

To obtain the heterogeneously catalyzed condensation reactions, the same amounts of reactants were used, but instead of anhydrous sodium acetate, 3 g of the 10 wt% supported KF catalyst (also containing 5 mmol of KF) was used. The mixture of solid catalyst and reactants was stirred in dichloromethane (3–5 ml) in a rotary evaporator for fifteen minutes to homogenize it, and then the solvent was evaporated off under vacuum to obtain a powdered dry solid, with the reactants adsorbed onto the solid surface. This operation must be done very carefully to avoid the evaporation of the acetic anhydride. One set of reactions was then conducted under conventional heating: the solid was placed in a round-bottomed flask and heated at reflux in a water bath for 1 hour (this operation can be carried out on the same rotary evaporator). Another set of reactions was conducted by microwave-assisted heating (15 minutes at 450 W), in an open Erlenmeyer flask (25 ml Pyrex glass) covered with a watch glass. In both cases, the reaction product was easily obtained after separation from the solid catalyst, by extraction with boiling acetone, (15 ml, 2–3 times); the extraction progress was followed by TLC analysis and after cooling and volume reduction by evaporation on a vacuum rotary evaporator, the crude azalactone was easily obtained by precipitation.

With respect to microwave irradiation, it is important to indicate that a total reaction time of 15 min corresponds, in fact, to 3 cycles of 5 min, with cooling periods (30 seconds) between them, which are used to monitor the reaction progress by TLC, so that the yields indicated in Table 1 were those optimized. In Table 1 both kinds of results obtained in the dry media condensation of *p*-hydroxybenzaldehyde with hippuric acid in acetic anhydride are collected, having been carried out using different 10 wt% supported KF catalysts. Table 5 shows the results obtained with different oxazolones by using the selected catalysts KF–AlPO<sub>4</sub> and KF–Al<sub>2</sub>O<sub>3</sub>, respectively.

Heterogeneously catalyzed condensation reactions with NaOAc–Al<sub>2</sub>O<sub>3</sub>-150 were carried out in exactly in the same way as with KF support catalysts.

The reuse of selected catalysts KF–AlPO<sub>4</sub> and KF–Al<sub>2</sub>O<sub>3</sub>, was investigated in the same reaction used in the screening of different supported KF catalysts. Thus, the synthesis of the azalactone 4-(4'-acetoxylidene)-2-phenyloxazol-5(4H)-one was successively carried out by the dry-media condensation (microwave and conventional heating, respectively) of *p*-hydroxybenzaldehyde with hippuric acid in acetic anhydride (1 : 1 : 4, molar ratio), by repeatedly using the same 3 g of 10 wt% KF support catalyst, after extraction of reaction products with boiling acetone, (15 ml, 3 times) and washing with dichloromethane (15 ml). The catalysts recovered by filtration can be directly used in a new reaction because no activation treatment is necessary

#### Spectroscopic data for products

**4-Benzylidene-2-phenyloxazol-5(4H)-one (1).** Mp 166 °C;  $\nu_{\text{max}}/\text{cm}^{-1}$  1794, 1652, 1555, 1450, 1165, 864, 768, 698; <sup>1</sup>H NMR (CDCl<sub>3</sub>)  $\delta$  7.28 (s, 1H), 7.45–7.75 (m, 6H), 8.15–8.35 (m, 4H); <sup>13</sup>C NMR (CDCl<sub>3</sub>)  $\delta$  126.6 (C), 129.0 (CH), 129.8 (CH), 130.1 (CH), 131.7 (CH), 132.0 (C), 133.3 (CH), 134.3 (CH), 134.4 (CH), 134.7 (C), 164.6 (C), 167.7 (C); HRMS (CI+) exact mass calcd. for C<sub>16</sub>H<sub>11</sub>NO<sub>2</sub> 249.07898, found: 249.07906.

**4-(4'-Acetoxybenzylidene)-2-phenyloxazol-5(4H)-one (2).** Mp 148 °C;  $\nu_{\text{max}}/\text{cm}^{-1}$  1796, 1759, 1659, 1593, 1550, 1236, 1165, 964, 880, 698; <sup>1</sup>H NMR (CD<sub>3</sub>COCD<sub>3</sub>)  $\delta$  2.32 (s, 3H), 7.18–7.24 (m, 2H), 7.25 (s, 1H), 7.47–7.64 (m, 3H), 8.14–8.26 (m, 4H); <sup>13</sup>C NMR (CD<sub>3</sub>COCD<sub>3</sub>)  $\delta$  21.2 (CH<sub>3</sub>), 122.1 (CH), 125.8 (C), 128.5 (CH), 129.0 (CH), 130.5 (CH), 131.3 (C), 133.4 (CH), 133.7 (CH), 152.9 (C), 163.8 (C), 167.5 (C), 168.8 (C); HRMS (CI+) exact mass calcd. for C<sub>18</sub>H<sub>13</sub>NO<sub>4</sub> 307.08446, found 307.08363.

**4-(2'-Acetoxybenzylidene)-2-phenyloxazol-5(4H)-one (3).** Mp 132 °C;  $\nu_{\text{max}}/\text{cm}^{-1}$  1794, 1763, 1709, 1667, 1598, 1536, 1165, 1362, 1162, 861, 756, 698; <sup>1</sup>H NMR (CD<sub>3</sub>COCD<sub>3</sub>)  $\delta$  2.42 (s, 3H), 7.29 (s, 1H), 7.34–7.70 (m, 4H), 7.90–8.95 (m, 5H); <sup>13</sup>C NMR (CD<sub>3</sub>COCD<sub>3</sub>)  $\delta$  20.9 (CH<sub>3</sub>), 117.0 (CH), 120.9 (C), 123.8 (CH), 125.5 (CH), 126.0 (CH), 126.6 (CH), 127.2 (C), 129.7 (CH), 130.1 (CH), 132.9 (CH), 134.6 (CH), 135.4 (CH), 151.9 (C), 165.4 (C), 166.4 (C), 169 (C); HRMS (CI+) exact mass calcd. for C<sub>18</sub>H<sub>13</sub>NO<sub>4</sub> 307.08446, found 307.08419.

**4-(4'-Methylbenzylidene)-2-phenyloxazol-5(4H)-one (4).** Mp 141 °C;  $\nu_{\text{max}}/\text{cm}^{-1}$  1794, 1652, 1605, 1493, 1162, 818, 695; <sup>1</sup>H NMR (CD<sub>3</sub>COCD<sub>3</sub>)  $\delta$  2.40 (s, 3H) 7.23 (s, 1H), 7.34 (d, 2H, *J* = 7.9 Hz), 7.61–7.72 (m, 3H); 8.15–8.23 (m, 4H) <sup>13</sup>C NMR (CD<sub>3</sub>COCD<sub>3</sub>)  $\delta$  21.7 (CH<sub>3</sub>), 126.6 (C), 128.9 (CH), 130.0 (CH), 130.5 (CH), 131.9 (C), 133.4 (CH), 134.2 (C), 142.8 (C), 164.0 (C), 167.8 (C); HRMS (CI+) exact mass calcd. for C<sub>17</sub>H<sub>13</sub>NO<sub>2</sub> 263.09463, found 263.09485.

**4-(2'-Methylbenzylidene)-2-phenyloxazol-5(4H)-one (5).** Mp 141 °C;  $\nu_{\text{max}}/\text{cm}^{-1}$  1794, 1648, 1598, 1551, 1291, 1160, 861, 768, 698; <sup>1</sup>H NMR (CDCl<sub>3</sub>)  $\delta$  2.51 (s, 3H) 7.25 (s, 1H), 7.31–7.36 (m, 2H), 7.47–7.62 (m, 4H), 8.16 (d, 2H, *J* = 7.4 Hz), 8.77–8.82 (m, 1H); <sup>13</sup>C NMR (CDCl<sub>3</sub>)  $\delta$  20.0 (CH<sub>3</sub>), 125.6 (C), 126.6 (CH), 128.4 (CH), 128.5 (CH), 128.9 (CH) 130.7 (CH), 131.2 (CH), 132.1 (CH), 132.2 (C), 133.2 (CH), 133.3 (C), 139.9 (C), 163.7 (C), 167.8 (C); HRMS (CI+) exact mass calcd. for C<sub>17</sub>H<sub>13</sub>NO<sub>2</sub> 263.09463, found 263.09516.

**4-(4'-Nitrobenzylidene)-2-phenyloxazol-5(4H)-one (6).** Mp 241 °C;  $\nu_{\text{max}}/\text{cm}^{-1}$  1796, 1655, 1596, 1559, 1520, 1343, 1165, 864, 667; <sup>1</sup>H NMR (CD<sub>3</sub>COCD<sub>3</sub>)  $\delta$  7.4 (s, 1H), 7.66–7.80 (m, 3H),

8.26–8.39 (m, 4H), 8.40–8.64 (m, 2H)  $^{13}\text{C}$  NMR ( $\text{CD}_3\text{COCD}_3$ )  $\delta$  124.1, 124.4, 127.9, 129.5, 130.7, 133.9, 135.2, 138.9, 148.1, 158.8, 165.9; HRMS (CI+) exact mass calcd. for  $\text{C}_{16}\text{H}_{10}\text{N}_2\text{O}_4$  294.06406, found: 294.06151.

**4-(4'-Chlorobenzylidene)-2-phenyloxazol-5(4H)-one (7).** Mp 197 °C;  $\nu_{\text{max}}/\text{cm}^{-1}$  1796, 1655, 1590, 1555, 1490, 1162, 826, 695;  $^1\text{H}$  NMR ( $\text{CD}_3\text{COCD}_3$ )  $\delta$  7.17 (s, 1H), 7.44 (d, 2H,  $J = 8.3$  Hz), 7.53–7.63 (m, 3H) 8.1–8.2 (m, 4H);  $^{13}\text{C}$  NMR ( $\text{CD}_3\text{COCD}_3$ )  $\delta$  125.8 (C), 128.5 (CH), 129.0 (CH), 129.3 (CH), 129.9 (CH), 132.1 (C), 133.5 (CH), 133.7 (C), 137.3 (C), 164.1 (C), 167.2 (C); HRMS (CI+) exact mass calcd. for  $\text{C}_{16}\text{H}_{10}\text{ClNO}_2$  283.04001, found 283.03953.

**4-(4'-Methoxybenzylidene)-2-phenyloxazol-5(4H)-one (8).** Mp 157 °C;  $\nu_{\text{max}}/\text{cm}^{-1}$  1790, 1652, 1598, 1513, 1266, 1162, 1030, 830, 695;  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  3.81 (s, 3H) 7.06–7.12 (m, 2H), 7.24 (s, 1H), 7.58–7.69 (m, 3H), 8.03–8.36 (m, 4H);  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ )  $\delta$  55.9 ( $\text{CH}_3$ ), 115.4 (CH), 126.6 (C), 127.5 (C) 128.8 (CH), 129.4 (C), 130.0 (CH), 132.0 (CH), 134.1 (CH), 135.2 (CH), 135.5 (CH), 156.8 (C), 163.3 (C), 167.6 (C); HRMS (CI+) exact mass calcd. for  $\text{C}_{17}\text{H}_{13}\text{NO}_2$  279.08954, found 279.08937.

**4-(3',4'-Methylenedioxybenzylidene)-2-phenyloxazol-5(4H)-one (9).** Mp 195 °C;  $\nu_{\text{max}}/\text{cm}^{-1}$  1779, 1648, 1486, 1451, 1266, 1165, 926, 864, 698;  $^1\text{H}$  NMR ( $\text{CD}_3\text{COCD}_3$ )  $\delta$  6.17 (s, 2H) 7.02 (d, 1H,  $J = 8.0$  Hz), 7.23 (s, 1H), 7.63–7.72 (m, 4H), 8.17–8.20 (m, 3H);  $^{13}\text{C}$  NMR ( $\text{CD}_3\text{COCD}_3$ )  $\delta$  103.1 ( $\text{CH}_2$ ), 109.5 (CH), 111.5 (CH), 126.7 (C) 128.8 (CH), 129.2 (C), 130.1 (CH), 130.4 (CH), 131.9 (CH), 132.3 (C), 134.2 (CH), 137.6 (C), 143.9 (C), 151.6 (C), 163.6 (C); HRMS (CI+) exact mass calcd. for  $\text{C}_{17}\text{H}_{11}\text{NO}_4$  293.06881, found 293.06999.

**4-(3'-Phenylpropenylidene)-2-phenyloxazol-5(4H)-one (10).** Mp 151 °C;  $\nu_{\text{max}}/\text{cm}^{-1}$  1787, 1640, 1598, 1451, 1331, 1162, 872, 695;  $^1\text{H}$  NMR ( $\text{CD}_3\text{COCD}_3$ )  $\delta$  7.18 (s, 1H) 7.21 (s, 1H), 7.31–7.49 (m, 4H), 7.59–7.72 (m, 4H), 8.03–8.16 (m, 3H);  $^{13}\text{C}$  NMR ( $\text{CD}_3\text{COCD}_3$ )  $\delta$  123.9 (CH), 124.1 (CH), 126.7 (CH), 127.9 (C) 128.6 (CH), 128.8 (CH), 129.8 (CH), 130.0 (CH), 130.8 (CH), 133.1 (CH), 133.9 (CH), 134.3 (CH), 135.1 (C), 137.1 (C), 138.1 (CH), 144.7 (CH), 145.7 (CH), 162.9 (C), 165.7 (C); HRMS (CI+) exact mass calcd. for  $\text{C}_{17}\text{H}_{13}\text{NO}_2$  275.09463, found 275.09470.

**4-(1'-Methyl-3'-Phenylpropenylidene)-2-phenyloxazol-5(4H)-one (11).** Mp 155 °C;  $\nu_{\text{max}}/\text{cm}^{-1}$  1779, 1632, 1559, 1447, 1173, 965, 880, 695;  $^1\text{H}$  NMR ( $\text{CD}_3\text{COCD}_3$ )  $\delta$  4.15 (d, 3H,  $J = 6.3$  Hz), 7.47–7.53 (m, 7H), 7.93–8.13 (m, 5H);  $^{13}\text{C}$  NMR ( $\text{CD}_3\text{COCD}_3$ )  $\delta$  41.8 ( $\text{CH}_3$ ), 127.0 (C), 128.1 (CH), 128.4 (CH) 128.6 (CH), 129.0 (CH), 129.3 (CH), 129.9 (CH), 130.4 (C), 132.2 (CH), 132.5 (CH), 133.6 (C), 134.2 (C), 135.3 (CH), 139.2 (CH), 167.7 (C), 171.4 (C); HRMS (CI+) exact mass calcd. for  $\text{C}_{19}\text{H}_{15}\text{NO}_2$  289.11028 found 289.10999.

**4-(But-2'-enylidene)-2-phenyloxazol-5(4H)-one (12).** Mp 154 °C;  $\nu_{\text{max}}/\text{cm}^{-1}$  1791, 1655, 1559, 1451, 1327, 1181, 860, 698;  $^1\text{H}$  NMR ( $\text{CD}_3\text{COCD}_3$ )  $\delta$  1.94 (m, 3H) 6.63 (m, 1H), 6.98 (m, 2H), 7.55–7.63 (m, 2H), 7.66–7.70 (m, 1H), 8.07–8.11 (m, 2H);  $^{13}\text{C}$  NMR ( $\text{CD}_3\text{COCD}_3$ )  $\delta$  19.5 ( $\text{CH}_3$ ), 126.8 (C), 127.9 (C), 128.0 (CH) 128.6 (CH), 130.0 (CH), 133.5 (CH), 133.9 (CH), 145.2 (CH), 162.6 (C), 167.2 (C); HRMS (CI+) exact mass calcd. for  $\text{C}_{13}\text{H}_{11}\text{NO}_2$  213.07898, found 213.07921.

**4-Cyclohexylidene-2-phenyloxazol-5(4H)-one (13).** Mp 128 °C;  $\nu_{\text{max}}/\text{cm}^{-1}$  2938, 2863, 1779, 1659, 1450, 1293, 1170, 979, 885, 704;  $^1\text{H}$  NMR ( $\text{CD}_3\text{COCD}_3$ )  $\delta$  1.68–1.81 (m, 6H), 2.83 (t, 2H,  $J = 6.1$  Hz), 3.02 (t, 2H,  $J = 5.9$  Hz), 7.26–7.54 (m, 3H), 8.01–8.06 (m, 2H);  $^{13}\text{C}$  NMR ( $\text{CD}_3\text{COCD}_3$ )  $\delta$  28.2 ( $\text{CH}_2$ ), 28.3 ( $\text{CH}_2$ ), 29.1 ( $\text{CH}_2$ ), 32.1 ( $\text{CH}_2$ ), 126.4 (C), 127.7 (CH), 128.8

(CH), 129.2 (C), 132.3 (CH), 159.3 (C), 161.2 (C), 165.6 (C); HRMS (CI+) exact mass calcd. for  $\text{C}_{15}\text{H}_{15}\text{NO}_2$  241.11028, found 241.11014.

## Acknowledgements

The authors gratefully acknowledge the subsidies granted by the Ministerio de Ciencia y Tecnología, DGI (Projet BQU2001/2605), and by the Consejería de Educación y Ciencia (Junta de Andalucía), Spain. The valuable help of Prof. M. Sullivan in the grammatical revision of the manuscript is also acknowledged.

## References

- (a) F. M. Bautista, J. M. Campelo, A. García, D. Luna and J. M. Marinas, *Amino Acids*, 1992, **2**, 87; (b) K. Gottwald and D. Seebach, *Tetrahedron*, 1999, **55**, 723; (c) J. Meiwes, M. Schudock and G. Kretzschmar, *Tetrahedron: Asymmetry*, 1997, **8**, 527; (d) D. Seebach, G. Jaeschke, K. Gottwald, K. Matsuda, M. Breuning and G. Bringmann, *Tetrahedron*, 1997, **22**, 7359; (e) C. Cativela, M. D. Diaz-de-Villegas, J. I. García and A. I. Jimenez, *Tetrahedron*, 1997, **53**, 4479; (f) E. Buñuel, C. Cativela and M. D. Diaz-de-Villegas, *Tetrahedron*, 1995, **32**, 8923; (g) D. Donati, A. Garzon-Aburbah, B. Natalini, C. Marchioro and R. Pellicciari, *Tetrahedron*, 1996, **52**, 9901.
- (a) F. Cavalier and J. Verducci, *Tetrahedron Lett.*, 1995, **36**, 4425; (b) S. N. Mitra, S. Dey, S. Karthikeyan and T. P. Singh, *Biopolymers*, 1997, **41**, 1997.
- (a) A. P. Martinez, W. W. Lee and L. Goodman, *Tetrahedron*, 1964, **20**, 2763; (b) M. L. Gelmi, F. Clerici and A. Melis, *Tetrahedron*, 1997, **53**, 1843; (c) A. H. Abd-el-Rahm, E. M. Kandeel, E. A. Abdel-Razik and I. A. El-Ghamry, *An. Quim.*, 1993, **89**, 237.
- (a) P. D. Croce, R. Ferraccioli and C. La-Rosa, *J. Chem. Soc., Perkin Trans. 1*, 1994, 2499; (b) R. Cannella, F. Clerici, M. L. Gelmi, M. Penso and D. Pocar, *J. Org. Chem.*, 1996, **61**, 1854; (c) R. Bossio, S. Marcaccini, R. Pepino and P. Paoli, *J. Heterocycl. Chem.*, 1994, **31**, 729; (d) I. Arenal, M. Bernabe, E. Fernandez-Alvarez, M. L. Izquierdo and S. Penades, *J. Heterocycl. Chem.*, 1983, **20**, 607.
- (a) A. C. Chikere, B. Galunsky, V. Schünemann and V. Kasche, *Enzyme Microb. Technol.*, 2001, **28**, 168; (b) J. Penalba, R. Puchades, A. Maquieira, S. Gee and B. D. Hammock, *Biosens. Bioelectron.*, 2000, **15**, 99; (c) M. A. Gonzalez-Martinez, R. Puchades, A. Maquieira, I. Ferrer, M. P. Marco and D. Barceló, *Anal. Chim. Acta*, 1999, **386**, 201; (d) S. Kojima, H. Ohkawa, T. Hirano, S. Maki, H. Niwa, M. Ohashi, S. Inouye and F. I. Tsuji, *Tetrahedron Lett.*, 1998, **39**, 5242; (e) G. T. Hermanson, G. R. Mattson and R. I. Krohn, *J. Chromatogr. A*, 1995, **691**, 113.
- (a) R. Filler, *Advances in Heterocyclic Chemistry*, ed. A. R. Katritzky, Academic Press, New York, 1954, ch. 4, p. 75; (b) J. W. Cornforth *Chemistry of Penicillin*, eds. J. R. Johnson and R. Robinson, Princeton University Press, Princeton, New York, 1948, p. 688; (c) H. E. Carter, *Organic Reactions*, Wiley, New York, 1946, ch. 3, p. 198; (d) S. P. Dhoubhadel, *J. Indian Chem. Soc.*, 1986, **63**, 757; (e) M. Kitazawa, R. Higuchi, M. Takahashi, T. Wada and H. Sasabe, *J. Phys. Chem.*, 1995, **99**, 14784; (f) S. Icli, H. Icil, S. Alp, H. Koc and A. McKillop, *Spectrosc. Lett.*, 1994, **27**, 1115; (g) A. Patra, G. Ghosh and P. K. Mukhopadhyay, *J. Indian Chem. Soc.*, 1987, **64**, 414.
- (a) Y. S. Rao and R. Filler, *Synthesis*, 1975, 749; (b) I. Arenal, M. Bernabe and E. Fernandez-Alvarez, *An. Quim.*, 1981, **77**, 56; (c) G. V. Boyd and P. H. Wright, *J. Chem. Soc., Perkin Trans. 1*, 1972, 909; (d) Y. S. Rao, *J. Org. Chem.*, 1976, **41**, 722.
- (a) E. Galantay, A. Szabo and J. Fried, *J. Org. Chem.*, 1963, **28**, 98; (b) T. Wieland and V. Georgi, *Liebigs Ann. Chem.*, 1966, **700**, 133; (c) C. Cativela and E. Melendez, *Synthesis*, 1978, 832; (d) C. Cativela, M. D. Diaz-de-Villegas and J. A. Galvez, *Tetrahedron Lett.*, 1999, **40**, 1027.
- P. S. Rao and R. V. Venkatratnam, *Indian J. Chem., Sect. B*, 1994, **33**, 984.
- M. Kidwai, R. Kumar and P. Kumar, *Indian J. Chem., Sect. B*, 1996, **35**, 1004.
- (a) J. H. Clark and D. J. Macquarrie, *Chem. Soc. Rev.*, 1996, 303; (b) *Supported Reagents and Catalysts in Chemistry*, eds. B. K. Hodnett, A. P. Kybett, J. H. Clark and K. Smith, Royal Society of Chemistry, Cambridge, UK, 1998; (c) G. W. Kabalka and R. M. Pagni, *Tetrahedron*, 1997, **53**, 7999; (d) J. M. Fraile, J. I. García and J. A. Mayoral, *Catal. Today*, 2000, **57**, 3; (e) F. A. H. Al-Qallaf, R. A. W. Johnstone, J.-Y. Liu and D. Whittaker, *J. Chem. Soc., Perkin Trans. 2*, 1999, 1421.

- 12 (a) C. Cativela, J. M. Fraile, J. I. García, J. A. Mayoral, J. M. Campelo, D. Luna and J. M. Marinas, *Tetrahedron: Asymmetry*, 1993, **4**, 2507; (b) F. M. Bautista, J. M. Campelo, A. García, D. Luna, J. M. Marinas, J. I. García, J. A. Mayoral and E. Pires, *Catal. Lett.*, 1996, **36**, 215.
- 13 (a) F. M. Bautista, J. M. Campelo, A. García, J. León, D. Luna and J. M. Marinas, *J. Chem. Soc., Perkin Trans. 2*, 1995, 815; (b) F. M. Bautista, J. M. Campelo, A. García, J. León, D. Luna and J. M. Marinas, *J. Prakt. Chem.*, 1994, **336**, 815.
- 14 (a) J. M. Campelo, A. García, F. Lafont, D. Luna and J. M. Marinas, *Synth. Commun.*, 1992, **22**, 2335; (b) J. M. Campelo, A. García, F. Lafont, D. Luna and J. M. Marinas, *Synth. Commun.*, 1994, **24**, 1345.
- 15 J. M. Campelo, A. García, D. Luna and J. M. Marinas, *Can. J. Chem.*, 1984, **62**, 638.
- 16 J. A. Cabello, J. M. Campelo, A. García, D. Luna and J. M. Marinas, *J. Org. Chem.*, 1984, **62**, 638.
- 17 (a) F. M. Bautista, J. M. Campelo, A. García, R. M. Leon, D. Luna, J. M. Marinas and A. A. Romero, *Catal. Lett.*, 1999, **60**, 145; (b) F. M. Bautista, J. M. Campelo, A. García, R. M. Leon, D. Luna, J. M. Marinas, A. A. Romero, J. A. Navio and M. Macias, *J. Mater. Chem.*, 1999, **9**, 827; (c) F. M. Bautista, J. M. Campelo, A. García, D. Luna, J. M. Marinas and A. A. Romero, *Appl. Catal.*, 1998, **166**, 39; (d) J. M. Campelo, A. García, D. Luna, J. M. Marinas, A. A. Romero, J. A. Navio and M. Macias, *J. Chem. Soc., Faraday Trans.*, 1994, **90**, 2265; (e) F. M. Bautista, J. M. Campelo, A. García, D. Luna, J. M. Marinas and M. R. Urbano, *J. Mater. Chem.*, 1994, **4**, 311.
- 18 (a) J. A. Cabello, J. M. Campelo, A. García, D. Luna and J. M. Marinas, *J. Org. Chem.*, 1984, **49**, 498; (b) F. M. Bautista, J. M. Campelo, A. García, R. Guardado, D. Luna and J. M. Marinas, *J. Chem. Soc., Perkin Trans. 2*, 1989, 493; (c) F. M. Bautista, J. M. Campelo, A. García, R. Guardado, D. Luna and J. M. Marinas, *J. Mol. Catal. A*, 1996, **104**, 229; (d) F. M. Bautista, J. M. Campelo, A. García, R. M. Leon, D. Luna, J. M. Marinas, R. A. Quiros and A. A. Romero, *Catal. Lett.*, 1998, **52**, 205.
- 19 M. S. Climent, J. M. Marinas and J. V. Sinisterra, *React. Kinet. Catal. Lett.*, 1986, **32**, 177.
- 20 J. M. Campelo, M. S. Climent and J. M. Marinas, *React. Kinet. Catal. Lett.*, 1992, **47**, 7.
- 21 (a) J. H. Clark and D. G. Corke, *Chem. Lett.*, 1983, 1145; (b) D. Villemin, *J. Chem. Soc., Chem. Commun.*, 1983, 1093; (c) J. Yamawaki, T. Kawate, T. Ando and T. Hanafusa, *Bull. Chem. Soc. Jpn.*, 1983, **56**, 1885; (d) D. Villemin and M. Ricard, *Synth. Commun.*, 1987, 1093; (e) Y. Nakano, S. Niki, S. Kinouchi, H. Miyamae and M. Igarashi, *Bull. Chem. Soc. Jpn.*, 1992, **65**, 2934.
- 22 (a) S. Caddick, *Tetrahedron*, 1995, **51**, 10403; (b) D. Villemin and A. Ben-Alloum, *Synth. Commun.*, 1990, **20**, 3325; (c) D. Villemin and A. Ben-Alloum, *Synth. Commun.*, 1991, **21**, 63; (d) D. Villemin, B. Martin and B. Garrigues, *Synth. Commun.*, 1993, **23**, 2251.
- 23 (a) J. H. Clark, S. R. Cullen, S. J. Barlow and T. Bastock, *J. Chem. Soc., Perkin Trans. 2*, 1994, 1117; (b) J. H. Clark, A. P. Kybett, D. J. Macquarrie, *Supported Reagents: Preparation, Analysis and Applications*, VCH, New York, 1992; (c) T. Ando, J. H. Clark, D. G. Cork, T. Hanafusa, J. Ichihara and T. Kimura, *Tetrahedron Lett.*, 1987, **28**, 1421; (d) T. Ando, J. H. Clark, D. G. Cork and T. Kimura, *Bull. Chem. Soc. Jpn.*, 1986, **99**, 3281; (e) T. Baba, *Catal. Survey Jpn.*, 2000, **4**, 17.
- 24 (a) J. H. Clark, *Chem. Rev.*, 1980, **80**, 429; (b) L. Rand, J. V. Swisher and C. J. Cronin, *J. Org. Chem.*, 1962, **27**, 3505.
- 25 (a) J. H. Clark, *J. Chem. Soc., Chem. Commun.*, 1978, 789; (b) T. Ando and J. Yamawaki, *Chem. Lett.*, 1979, 45; (c) H. Liu, H. Lu, P. Wang, P. Sun and F. Zhang, *J. Chem. Soc., Perkin Trans. 1*, 1990, 2624; (d) D. Jinchang, G. Hengjie, W. Jinzhu and L. Caizhen, *Synth. Commun.*, 1994, **24**, 301; (e) D. Abenhain, C. Ngoc-Son, A. Loupy and N. Ba-Hiep, *Synth. Commun.*, 1994, **24**, 1199.
- 26 (a) R. Debnath, *Mater. Lett.*, 1991, **11**, 193; (b) R. Liang and T. Nakamura, *Mater. Res. Bull.*, 1985, **20**, 1253.
- 27 (a) A. Bose, M. Manhas, M. Manta-Shah, V. Rahu, S. Bari, S. Newaz, B. Banic, A. Chaudhary and K. Barakat, *J. Org. Chem.*, 1991, **56**, 6968; (b) P. Goncalo, C. Roussel, J. M. Melot and J. Vébrél, *J. Chem. Soc., Perkin Trans. 2*, 1999, 2111.