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Eprints ID: 5817

**To link to this article:** DOI:10.2202/1542-6580.2183  
URL: <http://dx.doi.org/10.2202/1542-6580.2183>

**To cite this version:** Aribert, Nicolas and Camy , Séverine and Lucchese, Yolande and Condoret, Jean-Stéphane and Cognet, Patrick (2010) Cleaner Routes for Friedel-Crafts Acylation. *International Journal of Chemical Reactor Engineering*, vol. 8 (n°1). pp. A53 ISSN 1542-6580

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# Cleaner Routes for Friedel-Crafts Acylation

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# Cleaner Routes for Friedel-Crafts Acylation

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## Abstract

Friedel-Crafts acylation is among the most fundamental and useful reactions to yield aromatic ketones but it is one of the less acceptable in terms of unwanted polluting by-products or atom economy because of the overconsumption of catalyst which is used in stoichiometric quantities in the conventional process. This route is nevertheless widely used in the fine chemical industry.

In recent years, awareness of the impact of industrial activities on the environment has led chemists to work on new chemical routes, less dangerous and more environmentally friendly.

We considered here the acylation of a benzofurane derivative by an acyl chloride, as an intermediary step for a pharmaceutical product. In this study, one of the first alternatives was to replace conventional catalysts ( $\text{FeCl}_3$  or  $\text{AlCl}_3$ ), by reusable solid catalysts. Indeed, a wide variety of new solid catalysts, more efficient and less polluting, has now emerged (zeolites, ion-exchange resins. . .). In this work, these catalysts were first tested in “conventional” conditions, i.e., using an organic solvent (1,2-dichlorobenzene in our case), to determine the best one, in terms of reactivity, lifetime and reusability. The zeolite Y was found the most appropriate.

However, the use of an organic solvent still remains questionable and the use of supercritical carbon dioxide as the solvent was also considered. Its inherent properties include non-flammability, mild critical conditions, tuneable solubility near to the critical point and very low environmental impact. The reaction was operated using a continuous high pressure fixed bed. Results concerning yield and selectivity are presented.

**KEYWORDS:** supercritical  $\text{CO}_2$ , Friedel-Crafts acylation, heterogeneous catalysis, zeolite

## 1. INTRODUCTION

The Friedel-Crafts acylation of aromatic compounds is a major route for the synthesis of aromatic ketones. This reaction is an electrophilic substitution by acyl halides, anhydrides, carboxylic acids or esters with an aromatic substrate and is conventionally carried out using over-stoichiometric amounts of metal halides as catalysts. Despite the high production of unwanted polluting and corrosive by-products (HCl in this case), Friedel-Crafts chemistry is widely used in the manufacture of fine chemicals intermediates (pharmaceuticals, agrochemicals and fragrances) (Gore, 1964).

In recent years, the concept of “green chemistry” has lead chemical industries to develop new products, materials and chemical processes, less dangerous and more environmentally friendly.

In the case of Friedel-Crafts acylation, a major drawback is linked to the use of homogeneous polluting catalysts (Lewis acids:  $\text{AlCl}_3$ ,  $\text{BF}_3$ ,  $\text{ZnCl}_2$ ... or Brønsted acids:  $\text{H}_2\text{SO}_4$ ,  $\text{HF}$  ...) and alternative routes using solid catalysts (Corma, 1995; Jasra, 2003) are to be found). Nowadays, a wide variety of solid catalysts, more efficient and less polluting can be proposed, such as zeolites, ion exchange resins, heteropolyacids... Such solid catalysts can be easily separated from liquid products and, in addition, they offer the possibility of carrying out Friedel–Crafts reactions using a continuously operated fixed-bed reactor, rather than batch reactors. For the same production target, continuous flow reactors have smaller size than batch reactors, thus increasing safety and reducing capital cost.

The second drawback is related to the use of organic solvents, potentially toxic or polluting. Carbon dioxide used as the reaction solvent can be a good alternative to conventional organic solvents, because, in this case, it has no environmental impact. Its usefulness particularly in the field of chemical synthesis has been now amply demonstrated (Beckman, 2004; Rayner, 2007; Ghosh *et al.*, 2005; Patcas *et al.* 2007, Arunajatesan *et al.*, 2001; Hitzler *et al.*, 1998).

This article presents first experimental results obtained for a Friedel-Crafts acylation reaction using new kind of catalysts in supercritical carbon dioxide. The first part of this work has consisted in the determination of the most appropriate solid catalyst in terms of yield and selectivity of the reaction, using dichlorobenzene as the solvent. Secondly, a transposition of the reactants/solid catalyst system has been done using supercritical  $\text{CO}_2$  as the solvent and the reaction has been operated in a continuous high-pressure fixed-bed reactor.

## 2. EXPERIMENTAL

### 2.1 Materials

Different kinds of catalysts can be used to perform Friedel-Crafts acylation: zeolites, ion exchange resins, metallic oxides, heteropolyacids (HPA) and clays. This preliminary choice of catalyst was made according to their reported efficiency for different aromatic acylations (Jasra, 2003; Arata *et al.*, 2000; Choudhary *et al.*, 2000).

Zeolites types H-BEA, H-Y and H-MOR have been investigated for this reaction. Zeolites H-Y with SiO<sub>2</sub>/Al<sub>2</sub>O<sub>3</sub> molar ratios of 6, 15 and 200 and zeolites H-BEA with SiO<sub>2</sub>/Al<sub>2</sub>O<sub>3</sub> molar ratios of 27 were purchased from Tosoh as powder. Zeolite H-Y (SiO<sub>2</sub>/Al<sub>2</sub>O<sub>3</sub> = 15) was also purchased in pellet form (1.5mm diameter and 2-5mm length cylinders). Zeolite H-MOR with SiO<sub>2</sub>/Al<sub>2</sub>O<sub>3</sub> molar ratio of 12 was supplied by Tricat Zeolites GmbH. Amberlyst-15 (ion-exchange resin), phosphotungstic acid (HPA) and Montmorillonite K-10 (Clay) were all purchased from Sigma-Aldrich. All these catalysts were in their acidic H-form. The activation of the zeolites is done by calcination using the following procedure: the sample of catalyst is heated in a furnace with a heating rate of 4 °C.min<sup>-1</sup> from room temperature to 500°C and then maintained at this temperature during 6 hours

The metallic oxides (Ga<sub>2</sub>O<sub>3</sub>, Bi<sub>2</sub>O<sub>3</sub>, Fe<sub>2</sub>O<sub>3</sub> and In<sub>2</sub>O<sub>3</sub>) were obtained from Sigma-Aldrich.

The water content of solvents (1,2-dichlorobenzene and CO<sub>2</sub>) has to be as low as possible to avoid the degradation of the acyl chloride into the corresponding acid and HCl. 1,2-dichlorobenzene (anhydrous) was purchased from Sigma-Aldrich and CO<sub>2</sub> (water content < 7 ppm) was supplied by Air Liquide.

In the context of this study, which is done through a collaborative industrial contract, it is not possible to disclose the exact name of the involved molecules. Figure 1 shows the reaction scheme: the substrate (a benzofuran derivative) is acylated by an aromatic chloride.

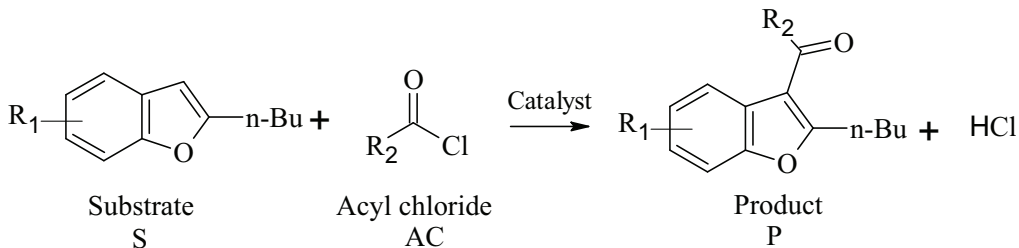


Figure 1. Reaction scheme

This lack of information about the involved molecules is not detrimental to the scientific aspect of the work, where this reaction is a model reaction to illustrate the concept of improving this kind of Friedel-Crafts type reaction.

## 2.2 Reaction procedure

### 2.2.a Operation using a conventional organic solvent

The acylation reactions were carried out in a 250 mL batch reactor equipped with a condenser and magnetic stirrer where the acyl chloride (AC), the aromatic substrate (AS) and the solvent (dichlorobenzene, S) were mixed inside the reactor. The different catalysts (note that in the case of zeolites, they were used directly after calcination) were then introduced into the reactor and the medium heated up to the reaction temperature. The resulting suspension was stirred under reflux for 6h.

Samples were taken periodically during the reaction with a syringe and assayed by HPLC (Waters 600E apparatus with Symmetry C8 column).

### 2.2.b Operation using supercritical CO<sub>2</sub>

The catalytic acylation reactions in supercritical conditions were performed in a continuous fixed-bed reactor, consisting of: (i) a supply unit, (ii) a reaction unit and (iii) an analytical loop (Fig. 2).

The supply unit comprised two HPLC pumps, one for the reactant liquid mixture, at a given ratio AS/AC, and one for liquid CO<sub>2</sub>. A static mixer (heated around 60°C) before the reaction unit allows good mixing of reactants and CO<sub>2</sub>.

The reaction unit comprised a tubular reactor with an internal cartridge (14mL cylinder, 0.50m length, 6mm inner diameter, closed by 3 μm fritted disks) filled with the solid catalyst, a safety rupture disc, a pressure transducer and a K-type thermocouple located inside the catalytic bed, near the outlet. Operation at the desired temperature, up to 500°C, is done using electrically heated shells around the tube, coupled to a PID temperature controller. The pressure is set using a mechanical back pressure regulator. The complete reaction unit was provided by Top Industrie, France.

Our system allows *in-situ* calcination of the catalyst. The calcination step is performed at 500°C during 6 h under air sweeping at a flow-rate of 250 mL.min<sup>-1</sup> (STP).

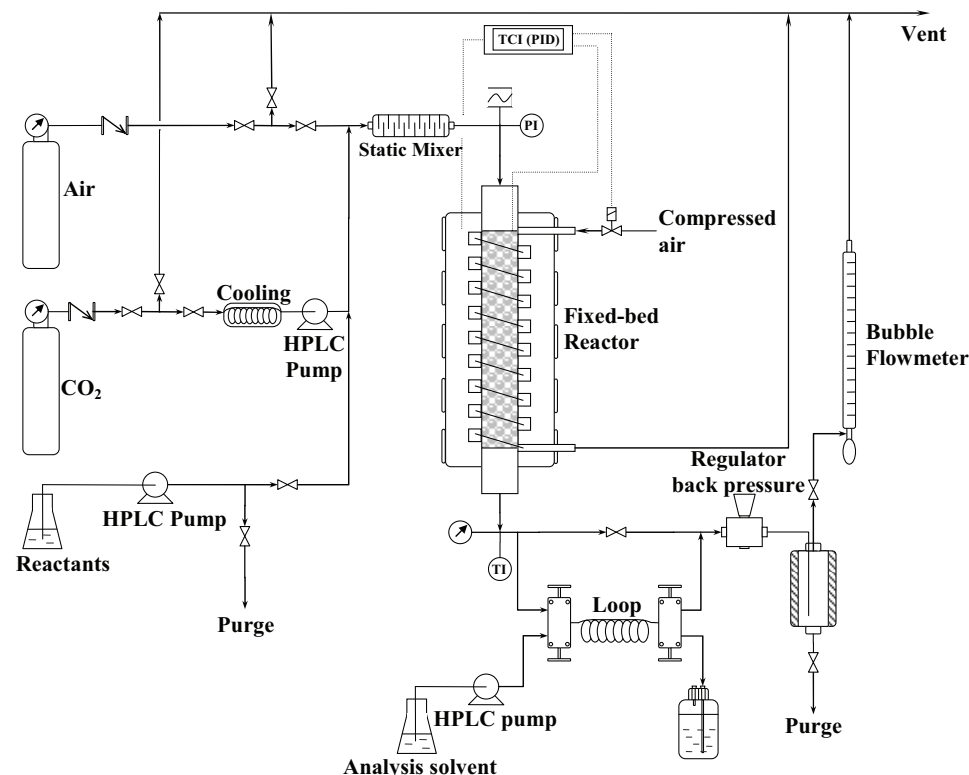


Figure 2. Scheme of the high pressure fixed bed (length 50 cm, inner diameter 6mm)

Continuous reactors for supercritical fluids offer the advantage over batch reactors that they do not require depressurisation to feed the reactants or to recover the products. In our system, samples can be taken out periodically during the reaction by using a sample loop of known volume. The obtained sample is then depressurized into the HPLC solvent and the loop is rinsed with 10 loop volumes of solvent. The HPLC analytic apparatus and procedure are the same as for the reaction in conventional solvent.

The procedure for operation of the continuous high pressure reaction is as follows:

- The cartridge is loaded with 4.3g of catalyst and calcined following the already described calcination procedure.
- Then the CO<sub>2</sub> is pumped to pressurize the system, and pressure is controlled by the back pressure regulator. The reactor is then heated up in the range 150-180°C, depending on experiments. When the temperature in the fixed bed is stabilized at the desired value, the mixture of the reactants is pumped into the CO<sub>2</sub> flow. Samples are taken at 30 min time intervals.

The flow of CO<sub>2</sub> was fixed to 1g.min<sup>-1</sup> or 2g.min<sup>-1</sup>, and the flow of reactants to 0.1g or 0.05g depending on experiments. The pressure was fixed at the technical maximum value of 300 bar, to minimize the loss of dissolving power of CO<sub>2</sub>, induced by the high temperature needed for the reaction.

### 3. RESULTS AND DISCUSSION

#### 3.1 Operation in dichlorobenzene

Table 1 presents the results of acylation performed in dichlorobenzene as the solvent over various solid acid catalysts at 180°C. Among these different kinds of catalysts, zeolite Y and Indium oxide appear to be the most efficient. Conversely, K-10 clay, HPA and H-Mor proved to be completely inactive, since no trace of product has been detected. Zeolite β, Amberlyst-15, bismuth oxide and iron oxide were found barely active.

Table 1: Acylation yields using different types of solid acid catalysts (10 mmol of AS; 10 mmol of AC; 50mL of dichlorobenzene, catalyst loading 1.0g, temperature 180°C)

Catalyst (SiO <sub>2</sub> /Al <sub>2</sub> O <sub>3</sub> )		Catalyst loading (g)	Surface area (m <sup>2</sup> /g)	Yield (time)
330 HUA	H-Y(6)	1	550	18% (6h)
360 HUA	H-Y(15)	1	600	45% (6h)
390 HUA	H-Y(200)	1	750	1% (6h)
930 NHA	H-β (27)	1	630	4% (6h)
TZM-1013	H-Mor (12)	1	475	NPD <sup>a</sup> (6h)
Resin	Amberlyst-15	1	53	6,3% (6h)
HPA	H <sub>3</sub> [P(W <sub>3</sub> O <sub>10</sub> ) <sub>4</sub> ]	1	4.6	0,2% (6h)
Oxide	Ga <sub>2</sub> O <sub>3</sub>	1	10-50	16,3% (3h)
	In <sub>2</sub> O <sub>3</sub>	1	25-50	44,1% (3h)
		0.1		42,2% (3h)
	Fe <sub>2</sub> O <sub>3</sub>	1	30-50	6,5% (3h)
	Bi <sub>2</sub> O <sub>3</sub>	1	10-50	1,6% (3h)
Clay	Mont. K-10	1	220	NR <sup>b</sup> (6h)

<sup>a</sup> NPD: No product detected



Table 1 indicates a very good activity for indium oxide, the yield being around 42% after 3 hours of reaction, even with a smaller amount of catalyst (0.1g), but reusability tests were not satisfactory. Indeed, it was not possible to recover the solid which seemed to have been solubilized in the medium of reaction.

So, zeolite Y (15) appears to be the best solid catalyst for this acylation reaction because high yields were obtained (45%) and no recovery problems have been observed. Note that the ratio  $\text{SiO}_2/\text{Al}_2\text{O}_3$  of the zeolite plays an important role because 6 and 200 ratios gave lower yields (respectively 18% and 1%).

Before operating this catalytic system in a continuous supercritical fixed-bed reactor, some additional experiments in dichlorobenzene were necessary to approach optimal operating conditions of the reaction. So AS/AC ratio, catalyst loading and catalyst reusability were further investigated. Indeed, preliminary results have shown that the maximal yield reaches 80% with 2g of zeolite Y (15) during 6 hours and that the reactant ratio is the main parameter, as shown on figure 3.

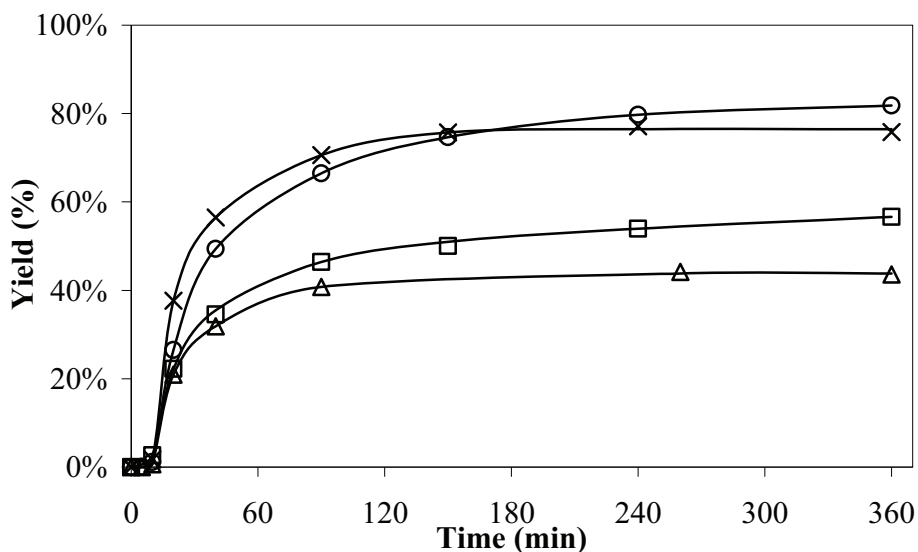


Figure 3. Effect of AS/AC ratio on yield (10mmol of AS; 10-100 mmol of AC; 50mL of dichlorobenzene; catalyst loading 2,0g; temperature 180°C), □ ratio 1/1, ○ ratio 1/1.5, + 1/4, △ ratio 1/10

The best yield has been obtained for an AS/AC ratio equal to 1 mol of substrate for 1.5 mol of acylating agent. Results are similar when the ratio AS/AC is increased to 1/4. But using a great excess of AC (ratio 1/10) seems to inhibit the activity of the zeolite. One hypothesis could be that active sites are saturated

by the AC. In fact this inhibition could also have been detected at the end of the curve with a ratio of 1/4 (around 4h) where kinetics stabilize unlike the experiment carried out with a 1/1.5 ratio, where kinetics slow down but do not stop. During these different experiments few by-products were generated. The only detected one was the anhydride form of the AC, which could be easily eliminated by simple post-reaction hydrolysis of the medium.

Another key parameter for industrial development deals with the reusability of the catalyst. After a single use and reuse after filtration on a fritted disc only, the yield drops significantly from 80 to 18% (see figure 4). The main reason of this deactivation phenomenon of the zeolite may be the deposition of heavy products, usually termed as “coke”. According to Richard *et al.* (1995) this “coke” probably results from the acylation of compounds obtained by condensation of aromatic substrates, thus blocking the active sites. Figure 4 also shows that the calcination of the used zeolite allows complete recovery of its catalytic activity. Indeed, the need for zeolite regeneration was already observed by Guignard *et al.* (2002) and Moreau *et al.* (2000). So the efficiency of regeneration (here by calcination) of the catalyst becomes a prominent parameter.

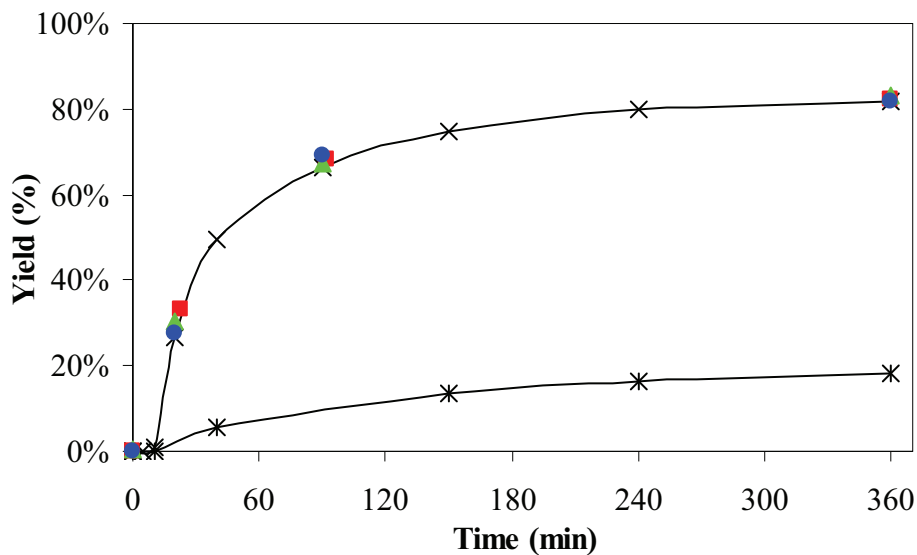


Figure 4. Reusability of zeolite Y (10mmol of AS; 20 mmol of AC; 50mL of S; catalyst loading 2,0g; temperature 180°C), × “fresh” calcined zeolite, \* reused zeolite, ■ zeolite once regenerated, ▲ zeolite twice regenerated, ● zeolite three times regenerated

Finally, these experiments using a conventional organic solvent have indicated that zeolite Y (15) is a suitable solid catalyst for the acylation reaction of the substrate. The next step of our study consists now in replacing dichlorobenzene by supercritical CO<sub>2</sub>, using zeolite Y (15) as the catalyst. To do so, a fixed-bed reactor has been designed in order to run the reaction in a continuous process.

### 3.2 Supercritical conditions

First experiments on the continuous set-up have been done with zeolite Y (15) in its powder form. Preliminary calculations, using Darcy's law, have estimated that the expected pressure drop in these conditions would be equal to 16 bar with a powder granulometry around 6-8 μm, and this value was found to be acceptable for an operating pressure above 200 bar. Experiments confirmed the value of the predicted pressure drop.

However use of zeolite powder proved to be very problematic, because all reaction runs ultimately led to clogging of the reactor, probably because the catalyst particles were indeed too small to be used in the fixed-bed reactor. Although duration of the experiments were not sufficient to be really representative because of clogging after a few hours, a 10% yield was typically observed (2g.min<sup>-1</sup> of CO<sub>2</sub>, 0.05g.min<sup>-1</sup> of reactants with a ratio AS/AC=1/2, T=180°C, P=200 bar).

Fortunately, zeolite H-Y (15) was also available in pellet form: 1.5 mm diameter and 2-5mm length cylinders, containing 20% of inactive binder clay ("Montmorillonite K-10"). Use of these pellets did not lead to clogging of the reactor. The pressure drop of the bed of pellets is expected to be much smaller and the observed pressure drop was mainly due to the 3 μm fritted disks at the ends of the tube, and did not exceed 5 bar.

Figure 5 presents the time course of the product concentration at the output of the fixed bed obtained using the sample loop. Note here the influence of the calcination pre-treatment where 15% yield, compared to 5% using fresh non calcined zeolite, is observed. Figure 5 also shows that the yield at the output declines rapidly after 60 minutes (maximal yield reached at this value of time).

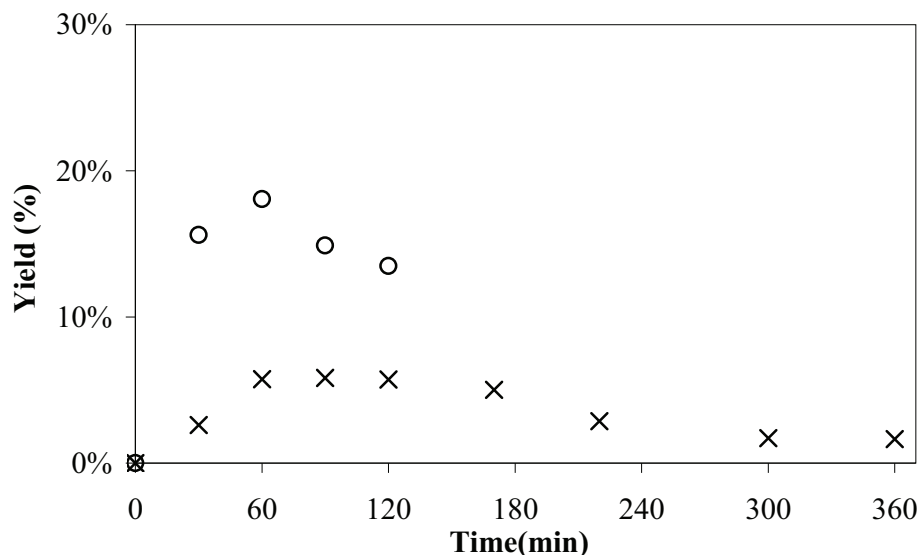


Figure 5. Yield of product with zeolite Y (15) in pellet form (2g/min of CO<sub>2</sub>, 0.05g/min of reactants with a ratio AS/AC=1/2, T=150°C, P=300bar), × non-calcined zeolite, ○ calcined zeolite

As a first hypothesis, these poor yield values could be attributed to the low solvating power of CO<sub>2</sub> in respect to reactants and/or products. Indeed, it is well known that the solvent power of pure CO<sub>2</sub> is low in respect to high molecular weight compound, as it is the case here.. Moreover, to insure significant activity of the catalyst, the temperature must be very high, and in spite of the high pressure in the process, this is not very favourable for a good solubility of the reactants and products in CO<sub>2</sub>. A comprehensive analysis of reactant solubility for the case of hydrogenation in supercritical solvents can be found in Pereda et al, (2002). To overcome this possible limitation, operation in mixtures of dichlorobenzene and CO<sub>2</sub> was considered. Figure 6 presents the computed phase diagram of the mixture dichlorobenzene-CO<sub>2</sub> at 150 °C. These results have been obtained using the Peng Robinson equation of state (PR EOS) with the value of binary interaction parameter  $k_{12} = 0.1175$  (from Stüber *et al.* (1996)). Computations were made using the Simulis software (ProSim S.A., France). This diagram shows that, at 150 °C and 300 bar, two kinds of mixtures are possible depending on the composition: for CO<sub>2</sub> mass fraction lower than 0.43, a low density liquid exists. Conversely, for CO<sub>2</sub> mass fraction higher than 0.71, the mixture is a dense gas. Between these two values, the mixture is a biphasic system.

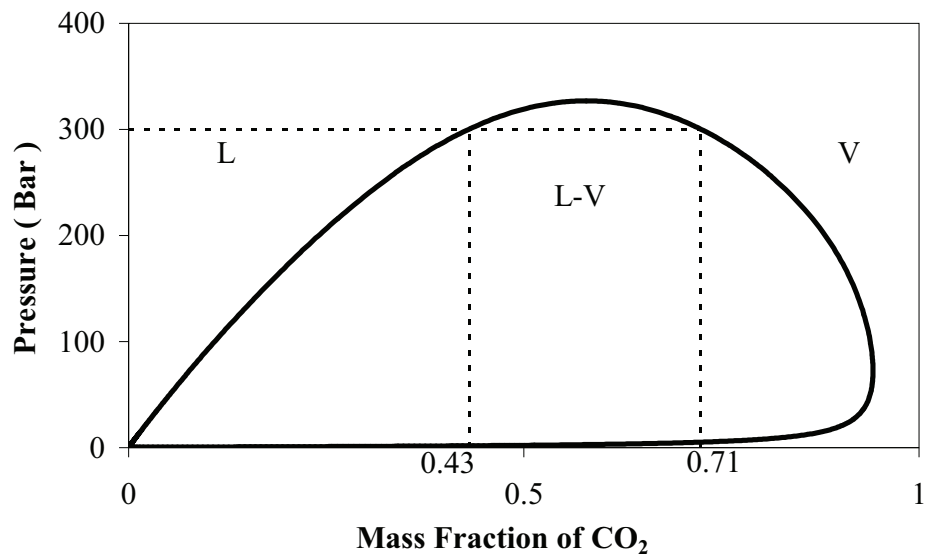


Figure 6: Isothermal fluid phase equilibrium diagram for  $T = 150^{\circ}\text{C}$   
 System: dichlorobenzene- $\text{CO}_2$  (computed using Peng Robinson EOS and  
 interaction parameter  $k_{12}=0.1175$  (value of  $k_{12}$  from Stüber *et al.*, 1996))

From this phase diagram, we performed the reaction in the two single-phase domains: the dense gas ( $\text{CO}_2$  rich) and the expanded liquid (dichlorobenzene rich). Experimental results are presented on figure 7. Using a low mass fraction of  $\text{CO}_2$  ( $\text{CO}_2$  mass fraction = 0.37, density = 1060 g/L, calculated with Peng Robinson EOS) no product was detected, whereas, with a homogeneous dense vapour phase of  $\text{CO}_2$  enriched with DCB ( $\text{CO}_2$  mass fraction = 0.72, density = 880 g/L, obtained with Peng Robinson EOS), a maximum 15% yield was obtained, despite occurrence of a rapid deactivation of the catalyst. This deactivation phenomenon seems to be slower with pure carbon dioxide. Note that in these experiments the zeolites have not been pre-treated by calcination

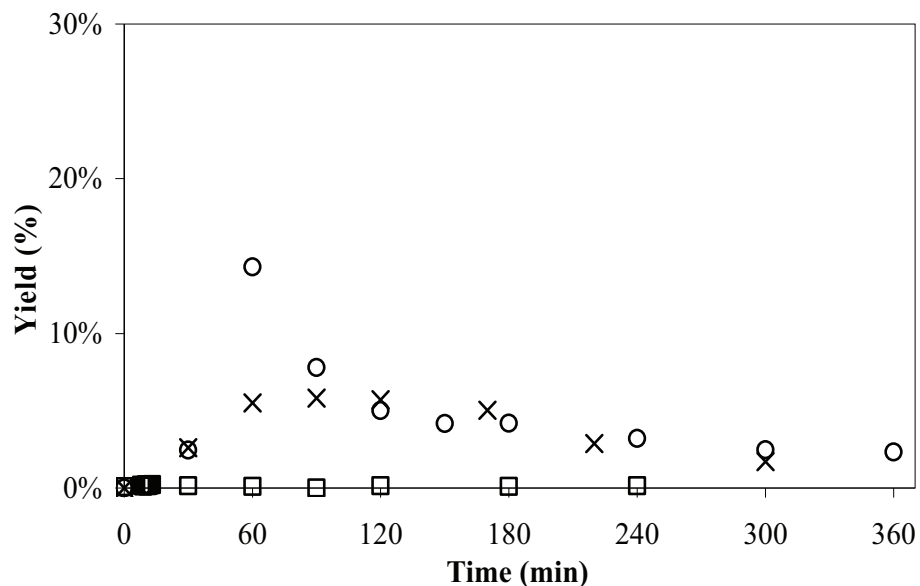


Figure 7: Yield of the product using H-Y zeolite in pellet form (0.05g/min of reactants with a ratio AS/AC=1/2, T=150°C, P=300bar), □ 1.92 g/min of dichlorobenzene-CO<sub>2</sub> (CO<sub>2</sub> mass fraction 0.37), ○ 1.8 g/min of dichlorobenzene-CO<sub>2</sub> (CO<sub>2</sub> mass fraction 0.72), × 2 g/min of pure CO<sub>2</sub>.

#### 4. CONCLUSION

From experiments in a conventional organic solvent (1-2 dichlorobenzene), zeolite Y (15) proved to be the more appropriate solid catalyst for the Friedel-Crafts acylation of a benzofurane derivative by an acid chloride. The different experiments carried out with zeolite Y (15) have given promising results, where few by-products were generated. The only detected one was the anhydride form of the AC, which could be easily eliminated by simple post-reaction hydrolysis of the medium.

In order to propose a cleaner process, with reduced use or total absence of an organic solvent, the reaction was tested in a continuous fixed bed reactor using supercritical carbon dioxide, or mixtures of carbon dioxide and dichlorobenzene, as the solvent. These experiments yielded interesting and encouraging results, even if rapid deactivation of the zeolite was observed. Note that a specific formulation of the catalyst, i.e., under pellet form, was necessary to operate the fixed-bed reactor without clogging. The deactivation phenomenon still need to be understood and might be improved by varying temperature or pressure. Although incomplete, these works are preliminary works to investigate new cleaner routes for this kind of chemistry and have demonstrated the feasibility of the approach.

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