CATALYTIC CYCLOCARBONYLATION IN COMPRESSED CARBON DIOXIDE: PRESSURE INFLUENCE OF CARBON MONOXIDE AND CARBON DIOXIDE

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Among the current interests in organic synthesis are those reactions performing multiple C-C bond formation, in special when they undergo under catalytic conditions¹. Due to its properties, there is a growing interest on the use of compressed fluids (CF) as solvent media in catalytic processes². In this context, we present herein studies that aim to the development of a cleaner technology for the preparation of cyclopentane derivatives by using the single step catalytic carbonylative cycloaddition, developed in our laboratory, using CO₂-expanded solvents instead of conventional liquid solvent media. In particular we have studied the effect of total pressure and carbon monoxide partial pressure over the yield of the reaction. This is a very efficient reaction, because at least three C-C bonds are achieved in a single operation in order to generate a cyclopentane derivate. The cyclopentane skeleton is present in numerous natural products, many of them bioactive^{3,4}.

INTRODUCTION

At present there is a growing interest on the use of CF, in liquid or supercritical state, pure or mixed with organic solvents, as sustainable solvents in synthetic processes, in particular, catalytic processes². Supercritical carbon dioxide ($scCO_2$) is one of the most attractive alternatives (total or partial substitution) to conventional organic solvents employed in industrial reactions; these organic solvents are often environmentally hazardous. Due to its properties, compressed fluids are especially attractive as solvents for the proposed catalytic processes: high miscibility with gases (*e.g.* CO), high diffusivity, low viscosity and tuneable solvent power allowing facile separation of catalysts and products (selective precipitation) by simple variation of pressure and/or temperature⁵. These properties offer great advantages to catalytic reactions: better solubility, influence on the kinetics, changes on the equilibrium constants, higher selectivities and yields, reduction of mass transfer limitations, etc.

The multiple C-C bond formation reactions (multicomponent reaction) are among the most important reactions in organic synthesis. So far, the application of those reactions has been limited to laboratory scale mainly due to: low yields in organic solvents, and difficult product separation¹. In this context, our group has been working for a long time on the carbonylative cycloaddition of allyl halides and alkynes mediated by nickel (**Fig. 1**).

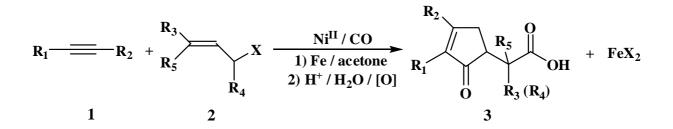


Figure 1: Catalytic carbonylative cycloaddition of alkynes and allyl halides in conventional solvents

In conventional organic solvents, the reaction gives high yields (70-90 %), takes place at room temperature and atmospheric pressure, is regioselective, and also stereoselective (when starting with and alkyne or allyl derivative that already has a stereocenter)³.

By using compressed fluids instead of conventional solvents, we expect to improve the selectivity as well as to diminish the use of organic solvents.

MATERIALS AND METHODS

The solubility behaviour of the different reactants was studied by a home made high pressure phase analyzer with sapphire windows, which allows visual inspection of the number of phases present. The agitation was accomplished by recirculation, due to the rectangular shape of the variable volume cell.

Materials

The catalyst employed for the reaction was prepared in-situ using: nickel bromide (98%, Aldrich), sodium iodide (98%, Panreac), and iron (powder, particle size 10 μ m, Merck) as the reducing agent. The substrates employed were allyl bromide (Aldrich, 99%) and phenylacetylene (Panreac, 97%). Carbon monoxide with a stated purity of 99.3% and carbon dioxide (ultra pure) were supplied by Carburos Metálicos. Acetone was previously distilled (under Ar) before each reaction.

Procedure

A new apparatus was designed and built in order to run the high pressure reactions. Reaction experiments were carried out batch wise at room temperature, and the kinetics were controlled by the decrease in total pressure.

In a typical experiment the reactor is manually charged with NiBr₂, NaI and Fe, and then sealed. The vacuum line is connected to the reactor in order to get rid of all the air. After that, acetone is introduced in the reactor. Carbon monoxide and carbon dioxide are introduced under different conditions (different partial pressures) for each reaction. CO₂ is introduced from the cylinder via a high pressure pump and CO directly from the cylinder (connected to a pressure regulator). At this point, we start with the mechanical stirring and wait so that the catalyst precursor could be formed insitu (prepared by a single electron reduction of a Ni(II) salt). Then, the substrates are slowly added by means of a high pressure pump. After that, the reaction is left running overnight. The following day the stirring is stopped, and gases inside the reactor are vented to atmosphere (in a fume hood). The product is collected with acetone and evaporated. After the work up, the reaction products are separated by flash chromatography, and identified and quantified by ¹H and ¹³C NMR.

RESULTS

This reaction is very sensitive to air and reduction time. Therefore, is very important to use the vacuum once the reactor is sealed and is also necessary to employ freshly distilled acetone to avoid any dissolved oxygen.

In respect to reduction time, we could observe in our experiments that $\frac{1}{2}$ hour reduction was the optimal time. Within that time, the Fe is able to reduce Ni^{II} (NiBr₂) to Ni^I free-radical-like species, which are quite reactive, hence allyl bromide can easily coordinate to the metal centre and catalysis can occur. Longer reduction times produced a deactivation of the catalytic system.

Solubility studies of catalysts and reactants in compressed carbon dioxide

Preliminary solubility experiments were performed on the different components (catalysts + reactants) involved in the cyclocarbonylation reaction, both in pure CO_2 and CO_2 -expanded acetone. So far, the results showed that the allyl halides and the alkynes tested were highly soluble both in pure CO_2 and CO_2 -expanded acetone under the studied conditions.

In the case of the catalyst, the solubility highly depends on the composition of the reaction medium $(CO_2/acetone)$. Thus, the reaction was feasible in the new media.

Effect of total pressure and carbon monoxide partial pressure

We have studied the effect of carbon dioxide solvent content and carbon monoxide partial pressure on yield and kinetics of the reaction schematized below (**Fig. 2**):

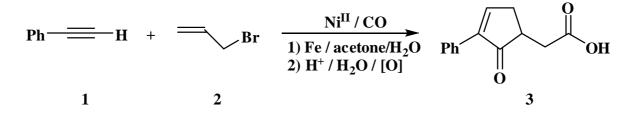


Figure 2: Ni-mediated carbonylative cycloaddition of allyl halides and alkynes

Since the kinetics of the reaction are followed by the decrease in CO pressure, we decided to do some preliminary kinetic studies without CO_2 and, based on these studies, 1.5 bar was chosen as the optimal CO partial pressure. Moreover, once we started slowly increasing the amount of CO₂, thus replacing the acetone up to CO_2 molar fractions of 0.8, two different types of behaviour were detected depending on the amount of CO_2 (solvent content) employed. When the reactions were carried out at low pressures, the effect of the dilution, caused by the addition of CO₂ in the system, was most relevant. Consequently, the reaction became slower compared to conventional reactions and either longer reaction time or higher CO pressure was needed in order to obtain high yields. On the other hand, at higher pressures, the miscibility effect is more important. Larger amounts of CO₂ are dissolved in the liquid phase (acetone + substrates + catalyst) where the reaction takes place, and since CO is so miscible with CO_2^6 , the amount of CO added in each reaction is crucial in terms of reactivity. At this point, we started to decrease the CO partial pressure down to 1 bar. Under these conditions we were able to perform the reaction at different working pressures (12 - 58 bars), and different solvent CO_2 molar fractions (0.22-0.83), without the need of increasing the reaction time. The reaction was also tested for other substrates. For instance, different alkynes were examined like trimethylsilylacetylene (bulky acetylene) or 2-ethyl butynoate (non-terminal acetylene), and similar yields to those achieved at conventional liquid conditions were obtained in both cases. Moreover, when using 2-norbornene (**Fig. 3**) instead of phenylacetylene, the reaction yield was highly improved in CO₂-expanded acetone, compared to the conventional reaction in acetone⁷, as well as the selectivity (~100%) towards the desired product **6**, in relation to 77% when using liquid acetone⁸. In all cases, the conventional organic solvent has been mostly replaced by dense CO₂.

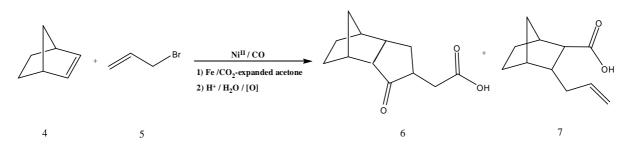


Figure 3: Catalytic cyclocarbonylation of 2-norbornene in CO₂-expanded acetone

CONCLUSION

In conclusion, we report here some studies of a highly efficient catalytic method to synthesize *intermolecularly* the cyclopentane skeleton starting from products as simple as allyl halides, alkynes, alkenes and carbon monoxide under very mild reaction conditions by means of a stoichiometric amount of iron, a catalytic amount of Ni halide and CO_2 -expanded acetone as the solvent.

The effect of carbon dioxide solvent content and total pressure over the reaction yield are currently under further study.

ACKNOWLEDGMENTS

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