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Heterogeneous copper catalysts for synthetic purposes

Building new simple bifunctional materials

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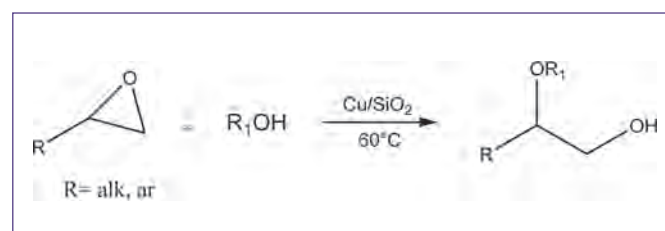
KEYWORDS

Copper catalyst; Bifunctional process; Solid acids; Epoxide opening; O-alkylation.

ABSTRACT

Highly dispersed copper oxide on silica reveals to be an effective acidic catalyst for the epoxide alcoholysis. The combination of acidic properties and hydrogenation activity when used in its reduced form makes the same catalyst an excellent system for the one-pot one-step O-alkylation of aromatic ketones and for the intramolecular cyclisation of γ -unsaturated ketones into ethers.

kind of substrates. However the activation or isomerisation of oxirane rings are linked with the use of Brønsted or Lewis acids as catalysts. Besides traditional homogeneous acids and metal complexes, some acidic solids (5), supported metal complexes (6) and MOFs (7) have been reported to promote the epoxide alcoholysis. The use of solid catalysts based on dispersed copper oxide over a simple chromatographic silica allows one to easily obtain β -alkoxyalcohols via epoxide opening (Scheme 1).



Scheme 1

In table 1 are summed up some selected results obtained in the epoxide opening with different alcohols.

Alcohol	Epoxide	Product	t (h)	Conv %	Sel %
2-PrOH			0.75	100	83
EtOH			2	99	90
2-butanol			0.5	98	83
iso-butanol			0.5	100	81
1-octanol			0.5	94	88
2-octanol			0.5	100	87
cyclohexanol			0.5	100	78
					1
2-PrOH			3	98	96
			0.75	100	100

Table 1. Epoxide alcoholysis promoted by CuO/SiO₂.

INTRODUCTION

The possibility to find new simple and reliable heterogeneous solutions in order to substitute traditional homogeneous acids would strongly improve the environmental impact and the economics of a chemical process. Moreover, the use of a solid catalyst could become a very important issue, due to the opportunity to design polyfunctional systems. The combination of several catalytic steps into a one-pot system promotes process intensification, thus decreasing the operating time and the amount of produced wastes (1). Here we would like to report about the use of heterogeneous copper catalysts as new acidic systems for the alcoholysis reaction of epoxides (2). The same catalyst also allows to do a significant step forward in setting up the one-pot one-step synthesis of asymmetrical ethers directly starting from an aromatic ketone and an aliphatic alcohol (3). On one hand the use of solid catalysts replacing homogeneous acids or metal complexes facilitates the crucial step of the product separation, particularly in the case of pharmaceutical intermediates. On the other hand the use of copper gives the additional advantage of avoiding the use of noble metals such as Pd, Pt and Rh that present the lowest tolerance limitations imposed by the European Medicine Agency, up to now one order of magnitude lower with respect to copper (4).

RESULTS AND DISCUSSION

Dispersed copper oxide as acidic catalyst

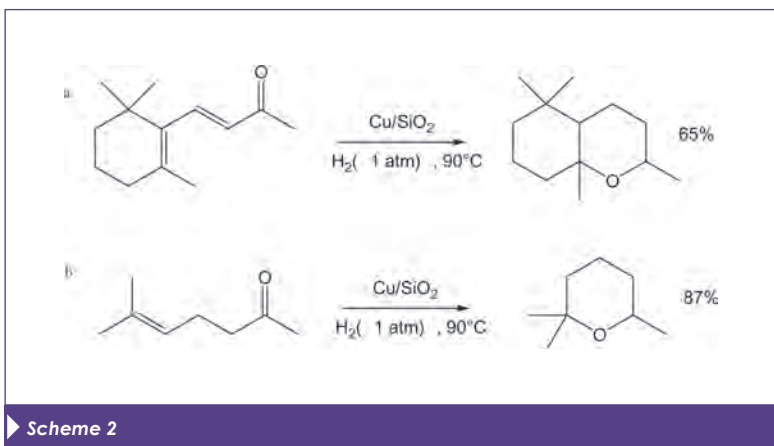
The opening of epoxides via nucleophilic attack represents a common way to the functionalisation of different

Catalyst	Alcohol	t (h)	Conv %	Sel %
SiO ₂	2-PrOH	18	2	0
CuO	2-PrOH	18	0	-
CuO/SiO ₂ IW	2-PrOH	18	33	-
CuO/SiO ₂	2-PrOH	0.75	100	83

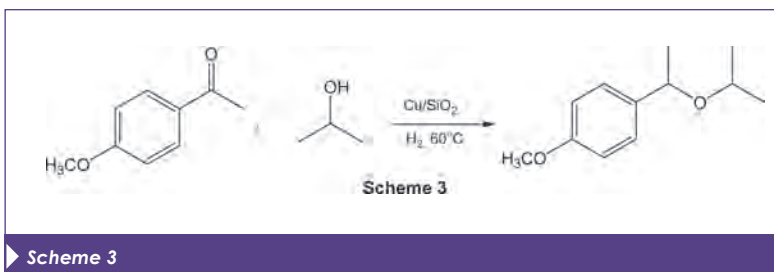
► Table 2. Styrene oxide alcoholysis with different catalytic systems (T = 60°C, 0.18 mmol Cu).


For the sake of comparison tests carried out with the bare silica, with bulk copper oxide and with a catalyst obtained by simple impregnation are also reported (Table 2).

Results obtained clearly show the outstanding properties of the catalyst both as far as activity and selectivity are concerned, demonstrating that the desired product can be obtained in short reaction times under very mild reaction conditions. Regioselectivity is almost complete (the main by-product being phenylacetaldehyde), thus showing that a prevalent S_N1 mechanism occurs. In the case of styrene oxide opening, the high activity observed by using bulky alcohols as nucleophiles is noteworthy, particularly if compared with other heterogeneous systems reported so far, whose performances significantly worsen when using alcohols others than methanol. Very good results were also obtained by varying the epoxide as the substrate, leading to the desired product with selectivities even higher with respect to β-alkoxyalcohols from styrene oxide. Moreover the catalyst is stable and reusable for at least five catalytic runs and results to be truly heterogeneous. The inactivity of both the bare silica and the



bulk copper oxide clearly shows that acidity derives from the presence of a highly dispersed copper oxide phase. The comparison with a catalyst prepared by traditional impregnation technique moreover demonstrates that the preparation method is peculiar for such an outstanding catalytic activity.





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The search for high dispersed systems in order to magnify the catalytic performances is a diffused and well set research topic in heterogeneous catalysis (8).

The chemisorption-hydrolysis technique used in the present case allows one to obtain very dispersed systems by means of a simple and reliable procedure, based on the use of available and homely materials, that means a commercial chromatographic silica and $\text{Cu}(\text{NO}_3)_2$. This makes the catalysts obtained with this technique highly appealing from the practical point of view, particularly if compared with more sensitive or sophisticated materials. Moreover silica supported copper oxide represents an atypical example, as heterogeneous acidic catalysts usually rely on the use of materials showing well defined acidic features such as -OH groups in zeolites and clays, or metal ions in Lewis acids like Sn-beta.

Reduced Cu/SiO_2 as efficient bifunctional system for O-alkylations

Copper supported on silica offers the opportunity to set up a bifunctional process by virtue of the hydrogenation activity of the metallic site when used in its reduced form, while also keeping the acidic properties observed for the unreduced catalyst in the epoxide opening.

These features lead to the formation of asymmetrical ethers starting from an aromatic ketone and an aliphatic alcohol in a one-pot one-step reaction. Ethers constitute an important class of organic compounds, in many cases related with the preparation of intermediates for the Flavour & Fragrances Industry (9). Heterogeneous copper catalysts have already been reported to be active in the synthesis of cyclic ethers by means of intramolecular reaction between ketones and

Catalyst	t (h)	Conv %	Sel %
4-OMe-phenylethanol as the substrate			
SiO_2	24	0	-
Cu/SiO_2	1.5	96	98
4-OMe-acetophenone as the substrate			
SiO_2	24	0	-
Cu/SiO_2	8	100	99

Table 3. Etherification reaction starting from 4-OMe-acetophenone or 4-OMe-phenylethanol and 2-propanol ($T=80^\circ\text{C}$, $P=\text{H}_2$ 1 atm).

of carbonyl compounds, useful precursors for aromatic substrates due to their availability via the Friedel Crafts acylation, an additional hydrogenation step is necessary. Cu/SiO_2 gives excellent results in the direct reaction of 4-OMe acetophenone with 2-propanol into the corresponding ether, a pleasant aniseed-like smell compound. In this case both hydrogenation and acidic activities can be traced back to the presence of dispersed copper phase. In fact the bare silica used under the same conditions starting from the two alcohols does not lead to any reaction. This point is not trivial, as bifunctional catalysts mainly rely on systems in which two

functions can be ascribed to two different sites (1), most often a metal site for hydrogenation and a zeolite as the support for acidic activity.

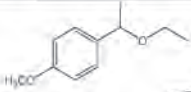
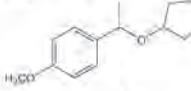
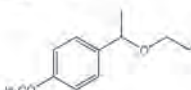
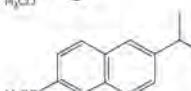
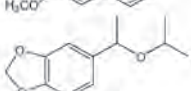
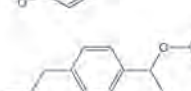
Nevertheless, the use of an acidic support allows one to obtain the same result by strongly improving performances of the catalytic system in terms of activity. In this way it is

possible to widen the substrate scope both by the ketone and by the alcohol side, thus making the reaction protocol highly general (Table 4). Preparation of asymmetrical ethers starting from the corresponding ketones and alcohols is reported to be promoted by few heterogeneous catalysts, mainly noble metal based systems requiring high pressure of H_2 (11) or water removal

solutions (12). The overall process results in an O-alkylation starting from simple precursors and avoiding the use of halides, bases or acids in solution and homogeneous complexes.

The reaction protocol results to be very interesting if we consider that heteroatom alkylation and arylation represent the most diffused reaction category (19 percent of total) in the synthesis of pharmaceutical products and intermediates, due to its important role in molecular construction (13).

Heterogeneous copper catalysts as new acidic systems for the alcoholysis reaction of epoxides

Alcohol	Substrate	Product	t (h)	Conv %	Sel %
Ethanol	4-OMe-acetophenone		5	100	97
Cyclopentanol	4-OMe-acetophenone		3	100	96
2-Ph-ethanol	4-OMe-acetophenone		7	70	89
2-propanol	5-OMe-acetonaphlone		7	100	98
2-propanol	3',4'- (methylenedioxy)acetophenone		16	100	95
2-propanol	4-tBu-acetophenone		16*	98	91

*T = 80°C

Table 4. Etherification reaction promoted by $\text{Cu}/\text{SiO}_2\text{-Al}_2\text{O}_3$ ($T=60^\circ\text{C}$, $P=1$ atm H_2).

EXPERIMENTAL SECTION

Copper catalysts were prepared by adding the support to a $(\text{Cu}(\text{NH}_3)_4)^{2+}$ solution prepared by dropping aqueous NH_3 to a $\text{Cu}(\text{NO}_3)_2 \cdot 3\text{H}_2\text{O}$ solution until pH 9 had been reached. After 20 min under stirring, the slurry, held in an ice bath at 273 K, was diluted with water.

The solid was separated by filtration, washed with water, dried overnight at 383 K, and calcined in air at 673K. Before reaction the catalyst was pre-reduced in-situ in H_2 (1 atm) at 270°C. $\text{SiO}_2\text{-Al}_2\text{O}_3$ (0,6 percent wt of Al_2O_3 , Pore Volume = 1.45 mL/g, Surface Area = 500 m^2/g) was kindly supplied by Grace Davison (Worms, D) and SiO_2 (PV = 0.75 mL/g, SA = 500 m^2/g) from Aldrich.

In a typical alcoholysis reaction a solution of the epoxide (0.8 mmol) in the alcohol (5 mL) is stirred with the solid catalyst (100 mg, 12 wt% Cu) at 60°C under nitrogen and the reaction mixture analysed by GC and GC-MS chromatography (5%-phenyl-methyl polysiloxane column).

A typical etherification reaction with the aliphatic alcohol as the solvent was carried out by filling the reactor containing the pre-reduced catalyst with a solution of 4-methoxyacetophenone (0.65 mmol) in 8 mL of alcohol and 1 atm H_2 .

The combination of several catalytic steps into a one-pot system promotes process intensification

CONCLUSIONS

Heterogeneous copper catalysts prepared by the simple and reliable chemisorptions-hydrolysis technique are effective solid acidic systems, able to substitute homogeneous systems in the opening of epoxides with alcohols.

Excellent system when reduced for the one-pot one-step O-alkylation of aromatic ketones.

With the same catalyst in the reduced form it is possible to promote cascade reactions, particularly useful in the transformation of polyfunctional substrates, that is the case of fine chemicals intermediates. The use of a non noble, non-toxic and non pyrophoric metal adds to the overall sustainability of the process.

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