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Selective hydrogenation of 4-(6-methoxy-2-naphtyl)-3-buten-2-one to Nabumetone®

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Abstract

Low loading copper catalysts allows hydrogenation of α,β-unsaturated ketones to the corresponding saturated ones with selectivity up to 99%. Moreover, the selectivity can be tuned toward different products only by playing with the support acidity or the experimental conditions. By using a 8% Cu/SiO_2 catalyst the final reduction step in the synthesis of the anti-inflammatory drug Nabumetone® can be carried out with selectivity >98% under mild conditions with good productivity and without any additives. No leaching of the metallic phase was observed, the catalyst is not pyrophoric even in the reduced state and it can be reused.

Keywords: Copper catalysts; Selective hydrogenation; α,β-Unsaturated ketones; Nabumetone®

1. Introduction

Catalytic hydrogenation has a long tradition in the area of fine chemicals production. No other reduction method has proved to be as versatile and industrially important, the most frequently used catalysts being those based on Pd on various supports, followed by Ni catalysts (mostly Raney type) and then by Pt, Rh and Ru ones.

We have long been involved in the selective hydrogenation of saturated or unsaturated carbonyl compounds to the corresponding alcohols over supported Cu catalysts.

In particular, cyclohexanones can be selectively reduced to the corresponding alcohols under very mild experimental conditions both using molecular H_2 [1] or a secondary alcohol [2] as hydrogen source (Scheme 1).

Moreover, aromatic ketones can be selectively reduced to the corresponding alcohols [3] or deoxygenated to the corresponding hydrocarbons [4] only by changing the catalyst support and the activation temperature (Scheme 2).

The strong attitude of Cu catalysts toward reduction of the C═O double bond allows chemoselective hydrogenation of unsaturated ketones (Scheme 3), although, the carbonyl group reduction ($\Delta H = -12$ kcal/mol) is thermodynamically unfavoured with respect to C═C double bond hydrogenation ($\Delta H = -30$ kcal/mol)[5]. For these reactions, the use of Cu/SiO_2 can be proposed as a valuable alternative to the use of complex metal hydride such as RedAl® or Vitride®, polymethylhydrosiloxane in the presence of zinc catalyst [6] or to dimethylphenylphosphine stabilized Cu(I) hydride [7].

On the contrary, α,β-unsaturated ketones can be very selectively reduced to saturated ones over low loading copper catalysts, obtaining very good results in this reaction by using a 8% Cu/SiO_2 catalyst supported on fumed, nonporous silica [8].

Here, we report an update on the hydrogenation of β-ionone **1** taken as a model for α,β-unsaturated ketones leading to a very selective and effective process for the hydrogenation of 4-(6-methoxy-2-naphtyl)-3-buten-2-one, a pharmaceutical intermediate.

2. Experimental

Copper catalysts, all with a metal loading of 8–9%, were prepared as already reported by adding the support to a solution containing $[Cu(NH_3)_4]^{2+}$ and diluting the slurry with water. The solids were separated by filtration, washed with water, dried

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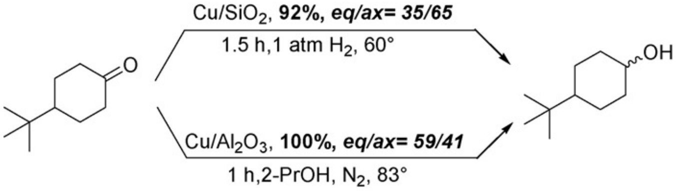
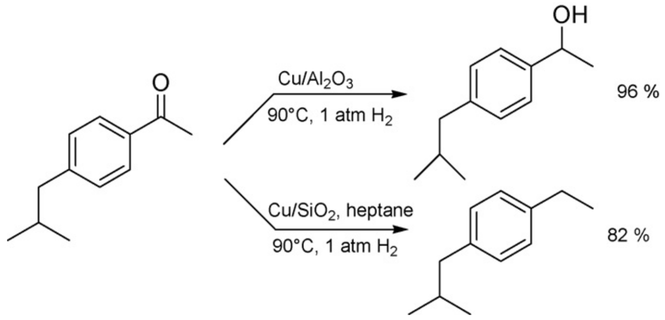
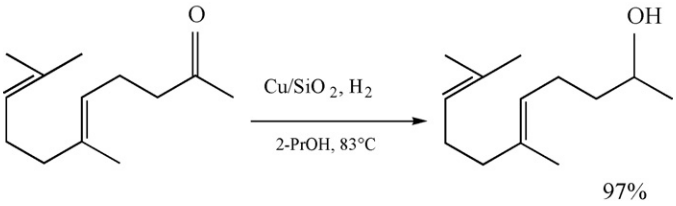


Scheme 1. Selective hydrogenation of cyclohexanones to the corresponding alcohols.



Scheme 2. Selective hydrogenation and deoxygenation of aromatic ketones.



Scheme 3. Chemoselective hydrogenation of unsaturated ketones over Cu catalysts.

overnight at 120 °C and calcined in air at 350 °C. The impregnated sample (Cu/SiO_2 IW) was prepared by adding an aqueous solution of $Cu(NO_3)_2$ of suitable concentration and volume to the support.

SiO_2 A (Aerosil®, BET = 380 m^2/g) was obtained from Degussa, SiO_2 B (BET = 320 m^2/g, *PV* = 1.75 ml/g), SiO_2 C (BET = 600 m^2/g, *PV* = 1.1 ml/g) and SiO_2 D (BET = 480 m^2/g, *PV* = 0.75 ml/g) were all from Grace Davison, Worms, D.

The catalysts were treated under vacuum at 270 °C for 20 min and then reduced under H_2 at the same temperature, removing under vacuum the water formed.

A solution of the substrate (100 mg) in toluene (8 ml) was transferred under N_2 in the reaction vessel containing the catalyst previously reduced. Catalytic tests were carried out at 90 °C at atmospheric pressure of hydrogen under magnetic stirring. Reactions at superatmospheric pressure were carried out in a 100 ml stirred stainless steel autoclave (0.6 g of 4-(6-methoxy-2-naphtyl)-3-buten-2-one in 50 ml toluene).

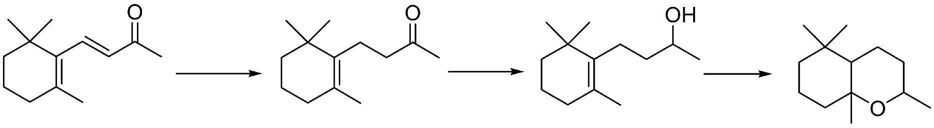
Reaction mixtures were analysed by TLC, GLC on a 5%-phenyl–95%-methyl-polysiloxane capillary column (30 m) and ^1H NMR.

Cu in the filtrate and in the product was found to be absent by GF AAS.

3. Results and discussion

Cu/Aerosil allowed us to obtain dihydro-β-ionone with selectivities between 95 and 100% at very high conversions (Table 1). However, a relevant amount of catalyst is required in order to complete the reaction in a few hours and the use of pyrogenic silica during the catalyst preparation may represent a drawback. Although in the hydrogenation of rapeseed oil no significant differences were observed, under the experimental

Table 1
Tuning of selectivity in the hydrogenation of β-ionone **1** over Cu/SiO_2 catalysts



1 **2** **3** **4**

		S/C (wt/wt)	t^a (h)	**2** (%)	**3** (%)	**4** (%)
1	Cu/SiO_2 (A)	0.7	2.5	99		
2	Cu/SiO_2 (B)	1	0.5	94		
3		1	24			65
4		1^b	9		95	
5		2	1	95		
6		4	2	97		
7		8	6	98		
8	Cu/SiO_2 (C)	4	3	92		
9	Cu/SiO_2 (D)	1	1.5		95	
10		4	3	90		
11		10	10	94		
12	Cu/SiO_2 IW	1	12	<5		

Heptane, 90 °C, 1 atm H_2.

[a] Time required to go to complete conversion.

[b] 2-PrOH as solvent.

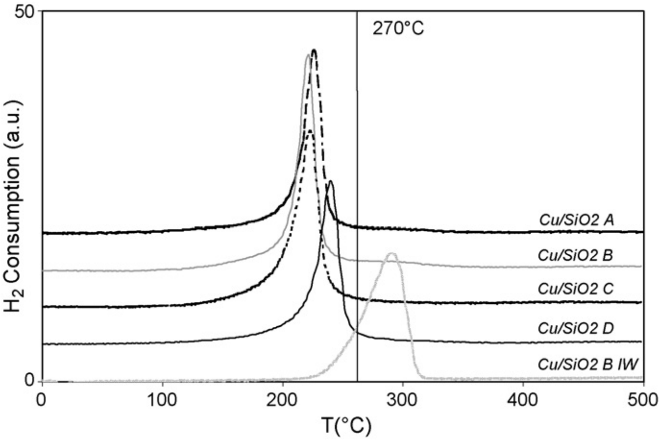


Fig. 1. TPR profiles of the different Cu/SiO_2 catalysts used.

conditions used, among several kind of silica tested as supports [9], in the case of α,β-unsaturated ketones significant improvements in productivity can be introduced by supporting the metal on different mesoporous silica gels. This not only leads to higher activity and yield in dihydro-β-ionone, but through the tuning of reaction conditions the Cu/SiO_2 catalyst allows to obtain different products with high selectivity. In particular, the catalyst prepared on silica B shows a very high activity together with a significant Bronsted acidity that allows the one pot transformation of β-ionone into tetrahydroedulane **4** through hydrogenation of **1** to **3** and nucleophilic attack of the OH to the C=C double bond (entry 3). The acidity can be poisoned by the use of an oxygenated solvent like 2-propanol giving dihydro-β-ionol **3** in very good yield but with very long reaction times. On the other hand, **3** can be obtained with higher productivity by using a less porous silica (entry 9).

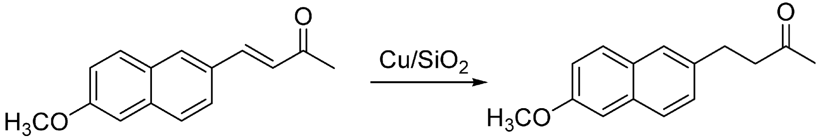
It is worth underlining that all three products are valuable ones in the Flavour & Fragrances industry. The selective hydrogenation of β-ionone to dihydro-β-ionone **2** can be carried out using a heterogeneous Raney Ni–Al alloy treated by sodium hydroxide in 89% yield [10], with a Ru-C catalyst [11] or with Ph_3SnH in benzene (94%) [12].

Dihydro-β-ionol **3** can be obtained from **1** in 80% yield by Birch reduction [13] or by hydrogenation over a Ti modified Pt catalyst [14] while tetrahydroedulanes can be obtained in three separate steps from α-ionone: (i) hydrogenation of α-ionone to dihydro-α-ionone over Raney Ni, (ii) selective reduction of dihydro-α-ionone to the alcohol with $LiAlH_4$ in Et_2O at 0 °C and (iii) formation of the ether catalyzed by conc. H_2SO_4 in toluene at 2–3 °C [15].

The high activity of these Cu/SiO_2 catalysts can be ascribed to the particular morphology of the metallic phase that in turn can be due to the preparation method [16]. Thus, characterization of Cu/B through FTIR spectra of adsorbed CO showed the presence of well formed crystallites exposing a significant fraction of step and edge sites particularly (1 1 1) microfacets, very efficient in H_2 dissociation [17]. These crystallites originate from the easy reduction of a well-dispersed CuO phase. A Cu/B sample prepared for the sake of comparison through conventional impregnation technique could be reduced only at much higher T, as evidenced by the TPR profiles (Fig. 1), and was found to be inactive under the experimental conditions used (entry 12).

Nabumetone [4-(6-methoxy-2-naphtalenyl)-2-butanone] is a nonacidic broad-spectrum anti-inflammatory, analgesic and antipyretic agent discovered by Smith–Kline–Beecham group and launched in 1985. With the growing popularity in the field of nonsteroidal anti-inflammatory drugs and due to the decrease in side effects induced by its use, in particular a lower toxicity

Table 2
Hydrogenation of 4-(6-methoxy-2-naphtyl)-3-buten-2-one over Cu/SiO_2 catalysts



Entry	Silica	*P* (bar)	S/C (wt/wt)	*t* (h)
1	Cu/SiO_2 (A)	1	4	7
2	Cu/SiO_2 (B)	1	4	3
3	Cu/SiO_2 (B)[a]	1	4	3
4	Cu/SiO_2 (C)	1	4	10
5	Cu/SiO_2 (A)	1	10	8
6	Cu/SiO_2 (B)	1	10	5.5
7	Cu/SiO_2 (C)	1	10	9
8	Cu/SiO_2 (A)	5	20	18
9	Cu/SiO_2 (B)	5	20	8.5
10	Cu/SiO_2 (C)	5	20	21
11	Cu/SiO_2 (B)	5	30	8
12	Cu/SiO_2 (B)[b]	5	30	10
13	Cu/SiO_2 (B)[c]	5	1	5

Selectivity always >98%.

[a] Catalyst recycled from entry 2.

[b] Catalyst activated *in situ* at 140 °C.

[c] Nonactivated catalyst.

Table 3
Hydrogenation of 4-(6-methoxy-2-naphtyl)-3-buten-2-one over Cu/SiO_2 and comparison with other catalytic systems

Entry	Catalyst	T (°C)	P (atm)	S/C (wt/wt)	t (h)	Sel. (%)
1	Cu/SiO_2 (B)	90	5	30	8	>98
2	5% Pd/C + K_2CO_3	50	4	40	3	99
3	5% Pd/C + K_2CO_3	25	1	11	12.5	98.5
4	0.15% Rh(TOA)/Al_2O_3	75	5	10	2.5	98.5
5	5% Rh/Al_2O_3	70	20	200	6	<98

to the gastro-intestinal tract, several synthetic strategies have appeared in the literature for the preparation of Nabumetone [18–21]. All of them involve the selective hydrogenation of a carbonyl conjugated C═C double bond.

This reduction can be carried out over Pd/C or over Ni Raney [22]. However, Raney catalysts are pyrophoric while supported noble metals can be pyrogenic, therefore concerns about safety in handling them are rising. Moreover, Pd can leach under catalytic hydrogenation conditions, thus representing a relevant problem for pharma end-products.

In the particular case of 4-(6-methoxy-2-naphtyl)-3-buten-2-one hydrogenation over Pd/C, the corresponding saturated alcohol is also formed. To maintain the inefficiency to this alcohol by-product at less than 5% basic compounds such as potassium carbonate, potassium hydroxide or the like are used [18,19].

Here, we wish to report that an 8% Cu/SiO_2 catalyst can be conveniently used in the hydrogenation of 4-(6-methoxy-2-naphtyl)-3-buten-2-one to Nabumetone® without the use of any additive.

Selected results obtained in the hydrogenation of 4-(6-methoxy-2-naphtyl)-3-buten-2-one over three different Cu/SiO_2 catalysts pre-reduced *ex situ* are reported in Table 2. By using a S/C ratio of 10 at 1 atm H_2, also in this case Cu/B performs better than the other two catalysts. The difference in activity is higher when working with S/C = 20 at 5 atm H_2 and only for Cu/SiO_2 B the S/C ratio can be increased to 30 without loss in activity.

Moreover, this catalyst does not need to be preactivated at high *T*, but it can be reduced *in situ* at 140 °C (Table 2, entry 12). At low S/C ratio, it can even be used without any preliminary treatment, showing that under these conditions, 90 °C and 5 atm H_2, CuO/B is reduced to the metallic phase also in solution.

Selectivity is very high: neither the unsaturated nor the saturated alcohol could ever been detected in the reaction mixture. It has to be noticed that the purification of Nabumetone from the hydrogenation by-products requires cumbersome procedures, such as the formation of hydrosulphite adducts [23]. Comparison with all the other catalytic systems (Table 3) shows that Cu/SiO_2 is an effective alternative for this hydrogenation. Moreover, it can be reused (Table 2, entry 3).

4. Conclusions

Supported copper catalysts with a low metal loading have shown to be an effective alternative to stoichiometric complex hydrides, Raney Ni and noble metal based catalysts in the hydrogenation of cyclohexanones, aromatic and unsaturated ketones to the corresponding alcohols. On the other hand, hydrogenation of α,β-unsaturated ketones over the same catalysts gave the corresponding saturated ketones with excellent yield even in the presence of other olefinic bonds. In the particular case of 4-(6-methoxy-2-naphtyl)-3-buten-2-one, the precursor of Nabumetone®, Cu/SiO_2 can be proposed as an effective alternative to Rh and Pd based systems. Even though it can be reused, the cost contribution of the catalyst is negligible and the recycle or recovery is not necessary to make the process competitive.

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