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Cu/SiO_2-catalyzed hydrogenation of cyclohexanones under very mild conditions

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Abstract—Unsubstituted and alkyl-substituted cyclohexanones, including 3-oxo-steroids, can be easily hydrogenated to the corresponding alcohols at 1 atm of H_2 and 60–90°C over a 8% Cu/SiO_2 non-toxic, reusable catalyst with excellent selectivity.

In the fine chemical industry, reduction of carbonyl groups mainly relies on the use of complex metal hydrides, sodium dihydrobis-(2-methoxyethoxy)-aluminate, commercialized as RedAl® or Vitride®, being one of most used.[1]

The catalytic hydrogenation of aliphatic ketones can be carried out in the presence of noble metals, usually Pt and Ru at 25–60°C and 1–5 atm H_2, or in the presence of Cu chromites and Ni catalysts. However, non-noble metal catalysts[2] require about 50 atm of pressure and temperatures higher than 100°C. Hydrogenation of 3-methyl-cyclohexanone e.g. has been reported to occur under 125 atm H_2 and 140°C in 2 h with a 5% by weight of catalyst[3] whereas a 1:1 catalyst/substrate ratio was needed to carry out the reduction at atmospheric pressure and room temperature.[4]

We already reported on the use of supported copper catalysts in the chemoselective hydrogenation of α,β-unsaturated ketones giving quantitative yields in the corresponding saturated ketone also when another olefinic bond is present in the molecule.[5] Saturated alcohols were formed only in a well separated step and often required the use of a higher pressure of H_2. Here we wish to report that hydrogenation of the carbonyl group in a series of substituted cyclohexanones can be conveniently carried out under very mild experimental conditions by using a supported 8% Cu/SiO_2 catalyst. Results obtained for a series of substituted cyclohexanones are reported in Table 1.

All substrates were reduced to the corresponding alcohols at 60 or 90°C and 1 atm H_2, reaction rates increasing with the number of alkyl groups. Preliminar tests on 4-*tert*-butyl-cyclohexanone showed that this substrate can be easily hydrogenated even at 40°C. This high activity is coupled with excellent selectivity towards alcohol formation. Thus, only for more substituted substrates less than quantitative yields were obtained, probably owing to formation of dehydration products (entry 5 and 6). However, in these cases evaporation of the solvent allowed to remove also volatile by-products and no further purification of the alcohol was needed.

The 3-oxo group of steroidal ketones was easily reduced, even at 60°C. This reduction was found to be selective with respect to the hydrogenation of a 17-oxo group (entry 9). It is also worth noting that this catalyst is much more active than the previously reported Cu/Al_2O_3, that was used in a 1:1 molar ratio.[6] Moreover Cu/SiO_2 was found to be reusable without loss neither in activity nor in selectivity (entries 3a–3c).

As far as stereoselectivity is concerned, the more stable epimer was always preferred at atmospheric pressure and 90°C, but a significant effect of the temperature was observed for the activated substrates. Thus, at 60°C important amounts of the axial epimer were formed particularly for 4-*tert*-butyl-cyclohexanone and 3,3,5-trimethyl-cyclohexanone (entries 5 and 6).

Preliminary experiments on a few open chain unsaturated ketones show this catalyst to be active and chemoselective also for such compounds.[7]

Keywords: copper catalysts; cyclohexanones; hydrogenation.

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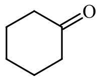
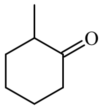
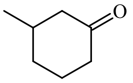
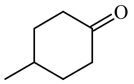
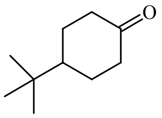
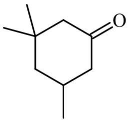
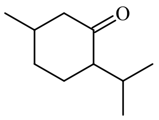
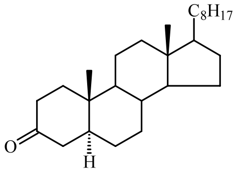
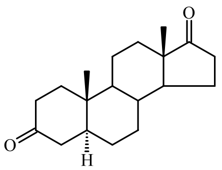
Table 1. Reduction of alkylcyclohexanones over Cu/SiO_2

Entry	Substrate	Exp.Conditions	Conv. %	Selectivity %	Eq/Ax ratio
1		n-heptane, 1 atm, 90°C, 3 h	100	92	-
2		n-heptane, 1 atm, 90°C, 48 h	0	-	-
		n-heptane, 6 atm, 90°C, 48 h	58	100	22/78
3		a) n-heptane, 1 atm, 90°C, 7 h	100	100	60/40
		b) n-heptane, 1 atm, 90°C, 7 h cat. recycled from a)	100	100	60/40
		c) n-heptane, 1 atm, 90°C, 7 h cat. recycled from b)	100	100	60/40
		d) n-heptane, 1 atm, 60°C, 7 h	100	100	63/37
4		n-heptane, 1 atm, 90°C, 3 h	100	100	65/35
5		n-heptane, 1 atm, 90°C, 1 h	100	90^a	58/42
		n-heptane, 1 atm, 60°C, 1.5 h	100	92	35/65
6		n-heptane, 1 atm, 90°C, 0.5 h	98	95	61/39
		n-heptane, 1 atm, 60°C, 1 h	100	95	24/76
7		n-heptane, 1 atm, 90°C, 1.5 h	100	100	50/50^b
8		toluene, 1 atm, 90°C, 2 h	100	93	58/42
		toluene, 1 atm, 60°C, 2.5 h	97	100	50/50
9		toluene, 1 atm, 60°C, 2.5 h	100	100	75/25

[a] Isolated yield.

[b] Menthol/neomenthol ratio obtained starting from a 80% menthone, 20% isomenthone mixture

Only 2-methyl-cyclohexanone could not be hydrogenated under these conditions (entry 2). This substrate was reduced only sluggishly even under 6 atm of H_2. As INDO calculations revealed that the carbonyl groups of 2-, 3- and 4-methyl-cyclohexanones are nearly identical in charge distribution,[8] this may be due to the steric hindrance of the equatorial methyl group inhibiting the access of the substrates to the active site. According to this hypothesis only *cis*-dihydrocarvone, with a methyl group at C2 but in axial position, was readily hydrogenated under mild conditions, leaving the *trans* isomer unaffected (Scheme 1).

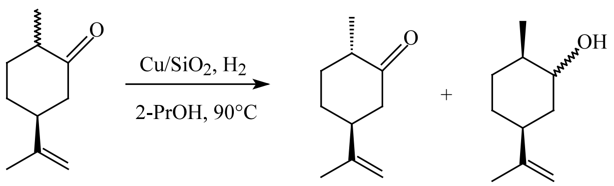
Molecular mechanics calculations showed that in the more stable conformers of both 2-methyl-cyclohexanone and *trans*-dihydrocarvone the carbonyl group and the methyl substituent are totally eclipsed.

Total chemoselectivity towards formation of the unsaturated alcohol was observed in the hydrogenation of *cis*-dihydrocarvone. However, 2-PrOH was the solvent of choice in order to avoid acid-catalyzed side reactions already observed with this substrate.[9]

The advantages of using Cu/SiO_2 instead of metal hydrides are quite evident. Thus, the latter are used in more than stoichiometric amounts, require time-consuming work-up procedures, produce a large amount of inorganic wastes and do not allow tuning of the configuration of the products. Moreover, this copper catalyst would be competitive also with Raney Ni that usually requires vigorous conditions unless large amounts of catalyst are used.[2,3,10] Furthermore, safety and environmental concerns claim for the use of this catalyst. We can suggest Cu/SiO_2 as an efficient alternative to metal hydrides and conventional copper and nickel catalysts.

Catalyst preparation: the catalyst was prepared as already reported[5] starting from a $Cu(NH_3)_4^{2+}$ solution obtained using $Cu(NO_3)_2·3H_2O$ as the precursor, but using a porous silica from Grace Davison (BET = 320 m^2/g, PV = 1.75 ml/g) as the support. In this way 8% Cu samples (BET = 263 m^2/g, PV = 0.78 ml/g), were obtained. The catalyst was reduced at 270°C with H_2 at atmospheric pressure, removing the water formed under reduced pressure, before the hydrogenation reaction. Very similar results were obtained using Degussa Aerosil 380 or another gel from Grace Davison (BET = 600 m^2/g, PV = 0.99 ml/g) as the catalyst support.

Experimental conditions: The substrates (100 mg) were dissolved in toluene or *n*-heptane dried over siliporites (8 ml) and the solution transferred, under H_2 into a glass reaction vessel where the catalyst (0.1 g for entries 1–7; 0.05 g for entries 8 and 9) had been previously reduced. Reactions were carried out at 90 or 60°C at atmospheric pressure with magnetic stirring. Reaction mixtures were analyzed by GC (mesitylene as internal standard). After completion the catalyst was filtered off, the solvent removed under reduced pressure and the equatorial/axial ratio evaluated by ^1H NMR spectroscopy. Recycling tests were performed starting from 0.4 g of substrate, washing the catalyst recovered with diethylether and reactivating it by hydrogenation before use. Isolated yields were determined on a 0.5 g scale experiment. HyperChem® Release 5.0 for Windows was used for molecular mechanics calculations.



Scheme 1.

Acknowledgements

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