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Meerwein–Ponndorf–Verley reduction of cycloalkanones over magnesium–aluminium oxide

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$MgO–Al_2O_3$ obtained from layered double hydroxide has been studied as a catalyst in the Meerwein–Ponndorf–Verley (MPV) reduction of cycloalkanones and substituted cyclohexanones in the liquid phase. Conversions for cycloalkanones always exceeded 95% and the selectivity was 100% within the first 10 h of reaction. In the MPV reduction of 4-*tert*-butylcyclohexanone to 4-*tert*-butylcyclohexanol a high stereoselectivity (*cis* : *trans* ratio > 12) was obtained. This stereoselectivity is explained by the transition-state selectivity imposed by the adsorption complex. For the reduction of cyclohexanone, a recycling test showed that the catalyst can be reused up to four times without losing more than 10% catalytic activity.

Introduction

A host of practical applications involving the reduction of carbonyl compounds by catalytic hydrogen transfer as a method for synthesizing alcohols have been reported in recent times. If the hydrogen donor used is an alcohol (*e.g.* propan-2-ol), the hydrogen transfer process is known as the Meerwein–Ponndorf–Verley (MPV) reduction. The MPV process allows the highly selective reduction of aldehydes and ketones under mild reaction conditions. Usually, a metal alkoxide such as aluminium isopropoxide is used as catalyst for the process. However, the catalyst must be used in a large excess in order to obtain acceptable yields and, in addition, eliminating the excess alkoxide once the reaction is complete can be rather difficult. Catalysts consisting of chelates of metals such as ruthenium,[1,2] iridium[3] or even rare earth elements such as samarium[4] and plutonium[5] have been tested as substitutes for conventional metal alkoxides; despite their advantages, however, these alternative catalysts are still difficult to remove at the end of the process and can rarely be reused.

In recent years, a variety of acid and basic heterogeneous catalysts have been successfully used for this purpose which avoid the need for removal from the reaction mass. Especially prominent among such catalysts are magnesium oxide[6,7] and zeolites.[8,9] Our research group has successfully used the MPV reduction of aldehydes of various kinds with basic solid catalysts such as magnesium and calcium oxides[10,11] and layered double hydroxides.[12]

This paper reports the results obtained in the reduction of cyclic ketones using secondary alcohols as hydrogen donors and a heterogeneous catalyst prepared from a magnesium–aluminium layered double hydroxide.

Layered double hydroxides, also known as hydrotalcite-like compounds, are anionic clays consisting of brucite-like $[Mg(OH)_2]$ layers where some Mg^{2+} ions are replaced with Al^{3+} or, in general, a trivalent ion. As a result, the layers exhibit a charge deficiency that is offset by anions in their interlayer spacing. The general formula for this type of compound is $[Mg_{1-x}Al_x(OH)_2]^{x+}[A_{x/m}]^{m-}\cdot nH_2O$, where A is the interlayer anion. The calcination of hydrotalcite-like compounds at temperatures above 400 °C produces a mixture of magnesium and aluminium oxides with surface basic properties that can be exploited in a variety of base-catalysed processes.[13–16]

Experimental

The basic catalyst employed was obtained using a previously reported method.[17] The layered double hydroxide or hydrotalcite-like compound was prepared from an aqueous solution containing 0.3 mol of $Mg(NO_3)_2\cdot 6H_2O$ and 0.15 mol of $Al(NO_3)_3\cdot 9H_2O$ (Mg : Al ratio = 2). This solution was slowly added dropwise to 500 ml of an Na_2CO_3 solution at pH 10 at 60 °C with vigorous stirring. The pH was kept constant by adding appropriate volumes of 1 M NaOH during precipitation. The suspension thus obtained was kept at 80 °C for 24 h, after which the solid was filtered off and washed with 2 l of de-ionized water. The resulting solid was denoted HT and was calcined at 500 °C for 8 h to obtain a mixture of magnesium and aluminium oxides that was labelled HT-500 and used as the catalyst. In all instances, the solid was calcined immediately prior to use.

In previous work, solids of a similar nature[17–19] were characterized in structural, textural and chemical terms, and found to exhibit surface basic properties.

The catalytic hydrogen transfer reaction was conducted in a two-necked flask furnished with a condenser and a magnetic stirrer. The secondary alcohol (0.06 mol) was treated with 0.003 mol of the ketone and the reaction mixture heated at reflux temperature with stirring (1000 rpm). The reaction was started by introducing 1 g of freshly calcined catalyst. Aliquots of the reaction mixture were collected at different times during the process and analysed by GC–MS using a Hewlett–Packard HP 5890 GC instrument furnished with a 30 m × 0.32 mm Supelcowax 10 column and an HP 5971 A MSD detector. The catalytic activity was calculated from the initial reaction rate corresponding to the slope of the conversion *versus* time curve. The initial reaction rate was calculated at conversion lower than 10% for which the curve is linear.

All chemicals used were purchased from Panreac, Merck or Aldrich and used without further purification.

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Table 1 Results obtained in the MPV reduction of cyclic ketones with propan-2-ol using catalyst HT-500

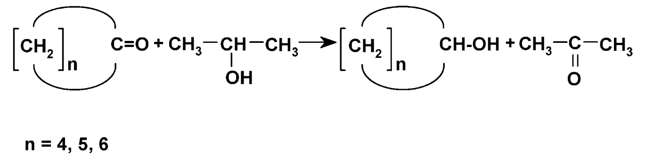
Ketone	*t*/h	Yield (%)	Selectivity	Catalytic activity (mmol cycloalkanol/h)
Cyclopentanone	10	94.6	100	0.800
Cyclohexanone	10	95.0	100	0.719
Cycloheptanone	10	92.1	100	0.685

Table 2 Results obtained in the MPV reduction of substituted cyclohexanones with propan-2-ol using catalyst HT-500

Entry	Ketone	*t*/h	Yield (%)	Selectivity	*cis* : *trans* ratio	Catalytic activity (mmol cycloalkanol/h)
1	Cyclohexanone	10	95.0	100	—	0.719
2	4-*tert*-Butylcyclohexanone	24	97.9	100	12.83	0.335
3	4-Methylcyclohexanone	10	94.7	100	5.22	0.595
4	3-Methylcyclohexanone	24	94.2	100	4.30	0.430
5	2-Methylcyclohexanone	24	42.6	100	0.95	0.153

Results

The MPV reduction of cycloalkanones with propan-2-ol takes place as depicted in Scheme 1. During the reaction, propan-2-ol is oxidized to acetone and the cyclic ketone is reduced to a cycloalkanol. Table 1 shows the yield, selectivity and catalytic activity obtained in the reduction of various cycloalkanones. As can be seen, the catalyst exhibited similar selectivity and yield with the three cycloalkanones. In all instances, the cycloalkanol yield after 10 h of reaction exceeded 90% and the selectivity was 100%. The catalytic activity decreased slightly with increasing ring size, as noted earlier; however, this resulted in no substantial difference in final yield or selectivity.



Scheme 1 Reaction scheme for the reduction of cycloalkanones with propan-2-ol using catalyst HT-500.

Let us now consider substituted cyclohexanones, which also react as depicted in Scheme 1. Table 2 shows the yield and selectivity for substituted cyclohexanols, as well as the catalytic activity obtained. The table contains an additional column listing the *cis* : *trans* isomer ratio obtained at the end of the reaction. Based on these data, the yield for 4-methylcyclohexanone was similar to that for cyclohexanone, even though the catalytic activity was considerably lower in the former case. On the other hand, with a much bulkier substituent (*e.g. tert*-butyl) at position 4 on the ring, the catalytic activity was nearly halved relative to cyclohexanone, so the reaction took 24 h to obtain a similar conversion. The insertion of a methyl group at position 3 gave rise to results similar to those obtained with a *tert*-butyl substituent at position 4. Finally, the presence of a methyl group at position 2 in the cyclohexanone resulted in a dramatic decrease in catalytic activity, which was nearly five times lower than that with unsubstituted cyclohexanone; as a result, the conversion at 24 h was very low (only 42.6%).

One other important aspect of the reduction of substituted cyclohexanones is the presence of stereoisomers in the reduction products. With a methyl substituent, the stereoselectivity of the process was higher with the group at position 4 than at position 2. It should be noted that the bulkier *tert*-butyl substituent resulted in higher stereoselectivity.

The reduction of cyclohexanone was also performed using alternative secondary alcohols as hydrogen donors. As can be seen from Table 3, the yields were excellent. The selectivity was 100% in all instances.

The study was finished by conducting catalyst reuse tests. The processes were carried out by filtering the catalyst off after the reaction and washing it with methanol several times. The catalyst was then calcined at 500 °C for 8 h. Fig. 1 shows the results obtained. As can be seen, the yield after 10 h of reaction was scarcely diminished—even after three reuses of the catalyst. The only apparent effect was a decrease in the catalytic activity.

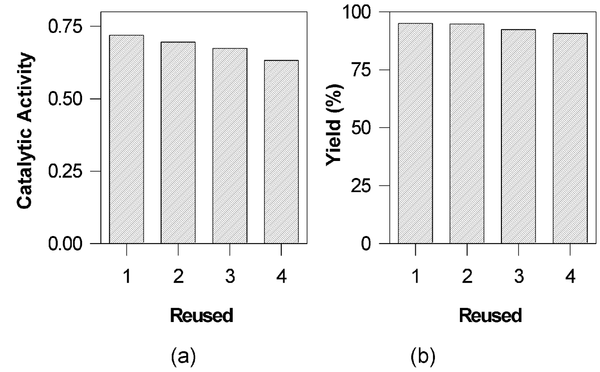
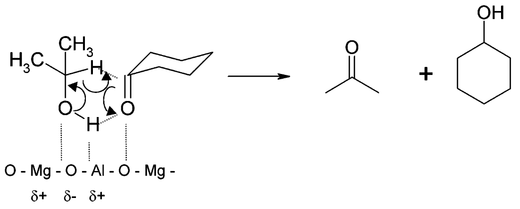


Fig. 1 Reuse of the catalyst in the MPV reduction of cyclohexanone with propan-2-ol: (*a*) variation of the catalytic activity (in mmol cyclohexanol/h); (*b*) percentage variation of the cyclohexanol yield.

Discussion

In previous work,[10,12] we accounted for the catalytic activity results obtained in the MPV reduction of various aldehydes with propan-2-ol with a mechanism similar to that reported by Ivanov *et al.*,[20] based on which the hydrogen transfer occurs *via* a concerted process that involves the formation of six-membered cyclic intermediate with the alcohol and the carbonyl compound adsorbed on the catalyst surface (Scheme 2).



Scheme 2 Reaction mechanism for the MPV reaction studied.

The rate-determining step of the process must be related to the interaction of the alcohol with the acid–base sites, which causes its dissociation to the corresponding alkoxide. Also, carbonyl compounds are known to interact with acid and basic sites on solid surfaces to give condensation reactions. In the proposed

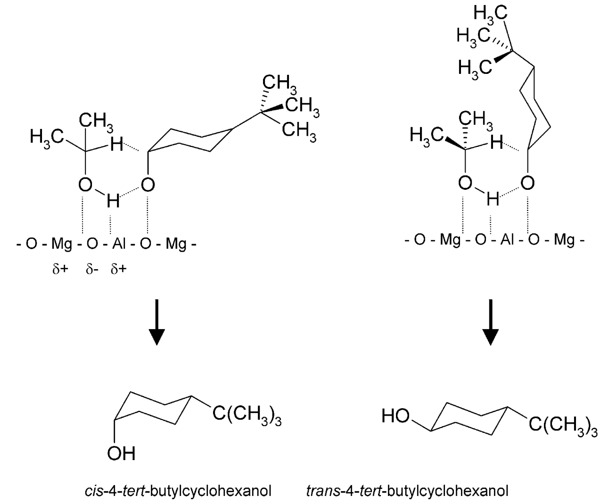
Table 3 Results obtained in the MPV reduction of cyclohexanone with alkan-2-ols using catalyst HT-500

Entry	Alcohol	*T*/°C	*t*/h	Yield (%)	Catalytic activity (mmol alcohol/h)
1	Hexan-2-ol	136	7	97.9	3.240
2	Pentan-2-ol	118	8	98.0	2.249
3	Butan-2-ol	98	8.5	96.1	1.559
4	Propan-2-ol	82	10	95.0	0.719
5	Hexan-3-ol	135	7	96.2	2.744
6	Pentan-3-ol	115	8	96.8	2.030

scheme, the isopropoxide formed from propan-2-ol transfers a hydride ion that attacks the carbon atom in the carbonyl group. The synchronous process illustrated in Scheme 2 yields a new alcohol and a new ketone as the result of the hydrogen transfer.

This mechanism is quite consistent with the results obtained in the reduction of cyclic ketones (Table 1). In fact, increasing the ring size in the ketone from five to seven atoms should result in no significant changes in the complex that is adsorbed on the catalyst other than steric hindrance; based on the results, the effect must be insubstantial as it only caused a slight decrease in catalytic activity and the yield at 10 h was close to 95% in the three cases. On the other hand, the substituted cyclohexanones exhibit marked differences as regards the adsorbed complex that result in substantial differences in both catalytic activity and yield (Table 2). In addition, the process produces stereoisomers. However, as shown below, the proposed model also accounts for these results.

The most immediate inference from the data in Table 2 is that introducing a methyl group onto position 4 in cyclohexanone (entry 3) seemingly has no decisive influence on the final reaction yield relative to unsubstituted cyclohexanone; in fact, the yield at 10 h was *ca.* 95% in both cases. When the substituent at position 4 is much bulkier (*e.g. tert*-butyl, entry 2), the catalytic activity decreases by more than 50% with respect to cyclohexanone. The reaction yield is also strongly affected; in fact, the reaction must be extended to 24 h to obtain results similar to those provided by cyclohexanone after 10 h. This suggests the presence of strong steric hindrance in the adsorbed complex, the effect obviously being much greater with 4-*tert*-butylcyclohexanone than with 4-methylcyclohexanone. In order to examine further the effect of steric hindrance, we conducted MPV reductions of 3- and 2-methylcyclohexanone (entries 4 and 5 in Table 2). A comparison of the results for the three methyl-substituted cyclohexanones reveals decreased yield and catalytic activity for the 4-substituted ketone in relation to the 2-substituted compound; this is consistent with the proposed mechanism since the presence of a substituent at position 2 must severely hinder the formation of the adsorbed complex (so much so that the yield at 24 h was only 42.6%). As noted earlier, the MPV reduction of substituted cyclohexanones produces stereoisomers of the reaction product. Accordingly, the next step in this work was to check whether the proposed mechanism would account for the experimental stereoselectivity results. Based on the data of Table 2, the 4-substituted cyclohexanones exhibited the best stereoselectivity results (particularly that with the bulky *tert*-butyl group). Based on the proposed mechanism, 4-*tert*-butylcyclohexanone can be adsorbed in the two ways shown in Scheme 3, which lead to a major isomer (*cis*) and a minor isomer (*trans*), respectively. The adsorbed complex that yields the *trans* isomer exhibits a stronger interaction between the methyl groups in propan-2-ol and the *tert*-butyl substituent than does the adsorbed complex leading to the *cis* isomer. As a result, 4-*tert*-butylcyclohexanol is obtained in a high *cis* : *trans* ratio. This ratio decreases on replacing the bulky *tert*-butyl group with a methyl group, which substantially decreases steric hindrance (and the *cis* : *trans* ratio for 4-methylcyclohexanol as a result). The *cis* : *trans* ratio for the 3- and 2-substituted methylcyclohexanones is even lower, so much so that 2-methylcyclohexanol is obtained as a virtually equimolar mixture of both stereoisomers. This is consistent with the proposed model since the two adsorbed complexes for 2-methylcyclohexanone are similar and lead to both stereoisomers.



Scheme 3 Transition states in the formation of *cis*-4-*tert*-butylcyclohexanol and *trans*-4-*tert*-butylcyclohexanol.

These results can also be explained from stereochemical considerations such as the fact that the preference for the equatorial attack, leading to the axial *cis*-alcohol, is favoured to reduce the interaction of the axial hydrogens in positions 3 and 5 with the incoming alcohol, a type of 1,3-diaxial interaction. The nature (*tert*-butyl or methyl) and the position (3 or 4) of the substituent modify the geometry and induce changes in the selectivity (the percentage of equatorial alcohol changes from 7 to 19%). When the substituent is in position 2 the situation is completely different, in this case, in the equatorial approach there is a steric interaction between the incoming alcohol and the methyl group in the equatorial position, so that both approaches have similar interactions and the stereoselectivity is very small. The presence of strong steric requirements in both axial and equatorial approaches accounts for the low yield obtained in this case.

As can be seen from Table 3, which shows the results obtained in the reduction of cyclohexanone with different secondary alcohols, all provided excellent results as regards both yield and catalytic activity. In the alkan-2-ol series, conversion decreased in the following sequence: hexan-2-ol > pentan-2-ol > butan-2-ol > propan-2-ol. Accordingly, hexan-2-ol would be the best choice; however, because the reaction temperature would be nearly 60 °C higher than that with propan-2-ol, additional thermal energy would have to be expended, not only during the process but also afterwards to remove the excess alcohol, and the hexan-2-one produced. Similar considerations apply to alkan-3-ols (hexan-3-ol and pentan-3-ol). As can be seen, there was no significant difference between the results provided by secondary alcohols with the OH group at position 2 or 3.

Finally, the reuse tests performed revealed that the catalyst can be recycled at least four times without losing more than 10% catalytic activity. Fig. 1 shows the conversion and catalytic activity obtained. In addition to the ease with which the reaction product can be isolated, this process therefore has two other substantial advantages over homogeneous catalysis: the ease of recovering the catalyst and the ability to reuse it.

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