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ABSTRACT

The reduction of different types of aldehydes and ketones were performed in the presence of isopropylalcohol (as solvent and hydride source) under microwave irradiation. It is proved that dehydrated Woelm chromatographic alumina supported KOH catalyses these transformations. Regioselectivity was observed in the reduction of cinnamaldehyde and chemoselectivity was observed in the reduction of carbonyl in the presence of nitro group.

The reduction of carbonyl compounds to the corresponding alcohols is an important transformation in organic synthesis[1] and because of its significant role the development of newer reductive protocols continues to receive attention in spite of the availability of numerous reagents.

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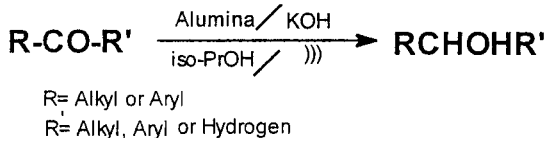
Hydrogenation of carbonyl compounds by hydrogen donors catalyzed by metal alkoxides[2] (especially aluminum alkoxide, Meerwein-Poundrof-Verley reduction, MPV) is a method that was very often used before the advent of metal hydrides as reducing agents. This method has real advantages over the hydride transfer agents and catalytic hydrogenation using molecular hydrogen, since it can be carried out on a large scale and under atmospheric pressure.

The use of alumina as catalyst and reagent in organic synthesis is increasingly widespread due to improved efficiency of many surface bound reagents.[3,4] Horner et al[5] have used chlorinated γ-Al_2O_3 in combination with a small amount of Al(iso-PrO)$_3$ as catalyst in the MPV reduction of benzaldehyde, cyclohexanone, and acetophenone by isopropanol. In the absence of Al(iso-PrO)$_3$, no reaction occurred. A large reaction rate enhancement was found by the addition of a strong base. Posner et al[6,7] reasoned that dehydration of alumina and then introduction of 2-propanol as hydride source in place of the removed water would produce novel alumina which is weaker reducing agent than sodium borohydride and which is at least as selective as sodium cyanoborohydrides and 9-borabicyclo [3.3.1] nonane. The four most serious drawbacks to general use of this reagent as a reducing agent are: 1) the high temperature (400°C) required for the alumina activation, 2) the relatively large amount of alumina (3–5 g/mmol of carbonyl substrate) required for effective substrate reduction, 3) the crude alcohol products (before purification) indicates a small amount of conjugated carbonyl absorption due to aldol condensation and 4) unlike aldehydes, reduction of ketones was achieved in low yields and in long reaction times.

Microwave heating and its application in organic chemistry for a variety of reactions have been developed successfully, and in the past few years there have been a tremendous amount of interest in this area. Remarkable decrease in reaction times and, in some cases, clean reaction and better yields have been reported with microwave irradiation.[8,9]



According to the above facts, the design of new systems for hydrogenation of carbonyl compounds by hydrogen donors in a mild and selective manner is a challenging and rewarding undertaking in organic synthesis and numerous catalysts have been reported.[10] We now wish to report that dehydrated Woelm chromatographic alumina supported KOH

can be used as an effective catalyst for this goal in the presence of isopropyl alcohol as a source of active hydride and solvent under microwave irradiation.

Alumina was activated by two different methods: by heating it in a quartz vessel at 400°C for 24 h[7] or by microwave irradiation in a commercial microwave oven (800W) for 5 min. The two kinds of activated alumina obtain show almost the same catalytic activity in the reduction reactions. The reducing system was easily prepared by addition of activated alumina to a suspension of KOH in isopropyl alcohol. Several reduction reactions were performed, at various powers and with different amount of potassium hydroxide and activated alumina, in order to find the most adequate condition for this reaction under microwave irradiation. The required mole ratio of KOH to substrate 0.5 : 1, weight ratio of activated alumina to substrate 2.5 : 1, and the maximum power output of 200W were found to be the optimal conditions.

The alumina/KOH system was cleanly and rapidly applied to the reduction of variety of ketones and aldehydes in isopropyl alcohol with a short time of microwave irradiation. The results are shown in Table 1. Thus the reduction of aromatic, alicyclic, and aliphatic ketones (Entries 1–13), aromatic and aliphatic aldehydes (Entries 14–26) afforded the corresponding alcohols in excellent yields. Position and electronic properties of substituents on the benzene ring do not influence appreciably the reactivities of aromatic aldehydes and ketones.

The successful reduction of acyloins (Entry 27) to their diols might extend the utility of the present simple procedure. By this method absolute selectivity is observed for the reduction of carbonyl functionality in the presence of a nitro group (Entries 15,16).

Selective 1,2 reduction of α,β-unsaturated carbonyl compound vs. 1,4 reduction is an important achievement for the synthesis of allyl alcohols from easily available α,β-unsaturated carbonyl compounds. Posner et al.[6,10] have applied γ-Al_2O_3 in the MPV reduction of unsaturated carbonyl compounds by isopropyl alcohol. However, rather high temperatures were needed (up to 300°C) and only low yields of alcohol were obtained due to the occurrence of several side reactions. We have studied the reduction of cinnamaldehyde with our system. The reduction is highly regioselective and only cinnamyl alcohol is isolated with high yield (Entry 28).

It is previously proved that strong bases are frequently added as promoters in H-transfer reactions since often they exert a beneficial effect on reaction rates.[11,12] Also, in our experiments, it was found that the presence of KOH in reaction media is essential, since the reaction in the absence of KOH, furnished only a trace of the product.

Table 1. Reduction of Ketones and Aldehydes to Alcohols with Isopropanol in the Presence of Activated Alumina in Basic Media Under Microwave Irradiation

Entry	Substrate	Product	Time (min)	Yield (%)
1	$PhCOCH_3$	$PhCHOHCH_3$	13	90
2	*p*-$ClC_6H_4COCH_3$	*p*-$ClC_6H_4CHOHCH_3$	12	91
3	$PhCOCH_2Br$	$PhCHOHCH_2Br$	11	92
4	PhCOPh	PhCHOHPh	13	87
5	$PhCH_2COCH_3$	$PhCH_2CHOHCH_3$	15	87
6	$PhCH_2COCH_2Ph$	$PhCH_2CHOHCH_2Ph$	16	85
7	Cyclohexanone	Cyclohexanol	12	88
8	Cycloheptanone	Cycloheptanol	13	87
9	$CH_3COCH_2CH_3$	$CH_3CHOHCH_2CH_3$	13	89
10	$CH_3COCH_2CH(CH_3)CH_3$	$CH_3CHOHCH_2CH(CH_3)CH_3$	14	86
11	$CH_3(CH_2)_5COCH_3$	$CH_3(CH_2)_5CHOHCH_3$	13	90
12	$CH_3CH_2CO(CH_2)_2CH_3$	$CH_3CH_2CHOH(CH_2)_2CH_3$	13	90
13	$CH_3COCH_2COCH_3$	$CH_3CHOHCH_2COCH_3$	13	89
14	PhCHO	$PhCH_2OH$	12	88
15	*m*-$NO_2C_6H_4CHO$	*m*-$NO_2C_6H_4CH_2OH$	9	93
16	*p*-$NO_2C_6H_4CHO$	*p*-$NO_2C_6H_4CH_2OH$	10	92
17	*o*-ClC_6H_4CHO	*o*-$ClC_6H_4CH_2OH$	11	92
18	*p*-ClC_6H_4CHO	*p*-$ClC_6H_4CH_2OH$	11	90
19	*p*-BrC_6H_4CHO	*p*-$BrC_6H_4CH_2OH$	12	91
20	*m*-$CH_3C_6H_4CHO$	*m*-$CH_3C_6H_4CH_2OH$	14	88
21	*p*-$CH_3C_6H_4CHO$	*p*-$CH_3C_6H_4CH_2OH$	13	90
22	*o*-$CH_3OC_6H_4CHO$	*o*-$CH_3OC_6H_4CH_2OH$	13	90
23	*m*-$CH_3OC_6H_4CHO$	*m*-CH3$OC_6H_4CH_2OH$	13	87
24	*p*-$CH_3OC_6H_4CHO$	*p*-$CH_3OC_6H_4CH_2OH$	12	89
25	2-Naphthaldehyde	2-Naphthylmethanol	14	88
26	$CH_3(CH_2)_6CHO$	$CH_3(CH_2)_6CH_2OH$	13	88
27	PhCOCHOHPh	PhCHOHCHOHPh	13	91
28	PhCH=CHCHO	$PhCH=CHCH_2OH$	12	88

a) Yields referred to isolated yields; b) Products were characterized by comparison of their physical data, IR NMR spectra with known samples.

To show the dramatic acceleration in the rate of reduction due to microwave irradiation, under the same experimental condition several aldehydes and ketones were heated just by conventional heating (82°C). However, only low yields of alcohols were obtained in comparably very long time. e.g., 1-phenyl ethanol was isolated from acetophenone at (10–12%, reflux, 24 h).

Transformation of benzaldehyde was performed also on a 100 mmol (10.6 g) scale to illustrate application of this method to preparation of gram

quantities of alcohols. Benzyl alcohol is obtained without appreciable decrease in the yield as compared to that obtained by the small scale experiment.

Although, the MPV reduction of aldehydes using aluminum alkoxide often gives significant amounts of aldol, Tishchenko, and Cannizaro condensation products[11] and in the application on dried Woelm alumina, the product is contaminated by conjugated carbonyl compounds due presumably to aldol condensation.[6] In our method, infrared analysis of the obtained products does not indicates any conjugated carbonyl by-product adsorption due to aldol condensations.

Compared to some previously reported reagents with major or minor drawbacks, several noteworthy features of this reagent are apparent: easy work-up procedure, availability of the reagent, operational simplicity, selectivity, use of inexpensive reagent, and high yields of products in considerably short reaction time. Therefore, we feel that it may be a suitable addition to the currently available methodology.

EXPERIMENTAL

General: IR spectra were recorded on a Shimadzo 450 spectrophotometer, ^{1}H NMR spectra in $CDCl_3$ on a Bruker Avance DPX instrument (250 MHz). Required carbonyl compounds were purchased from Fluka and Merck. Alumina 60 G neutral (Type E, Art. 1090) was purchased from Merck. Products were characterized by comparison of their physical data, IR and ^{1}H NMR spectra with known samples. The purity determination of the products and reaction monitoring were accomplished by TLC on silica gel polygram SILG/ UV 254 plates.

Dehydration of Alumina and General Procedure for the Reduction of Carbonyl Compounds

Alumina (1.5 g) was taken in a Pyrex Erlenmeyer flask (25 mL) and irradiated in a commercial microwave oven (800W) for 5 min. It was then allowed to reach room temperature. Fine powdered potassium hydroxide (0.14g, 2.5 mmol) was thoroughly mixed with the activated alumina (1.33 g) and the resulting powder was taken in a Pyrex round bottomed flask (25 mL) equipped with a reflux condenser (reflux condenser was outside the microwave oven) containing 15 mL of isopropyl alcohol. Carbonyl compound (5 mmol) was added to the resulting mixture and then irradiated in a commercial microwave oven (200W) for 9–16 min. The progress of the

reaction was monitored by TLC. The reaction mixture was then allowed to reach room temperature and neutralized with HCl (5%). The reaction mixture was filtered and the combined filtrate was extracted with dichlomethane (2×15 mL). The organic layer was dried over anhydrous sodium sulfate and solvent evaporated under reduced pressure to afford the TLC and ^{1}HNMR pure products in 85–93% isolated yields.

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