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Monoalkylations with alcohols by a cascade reaction on bifunctional solid catalysts: Reaction kinetics and mechanism

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ABSTRACT

A bifunctional catalytic system formed by Pd on MgO catalyzes the cascade process between benzyl alcohol and phenylacetonitrile, diethylmalonate and nitromethane, to give the respective α-monoalkylated products without external supply of hydrogen. The process involves a series of three cascade reactions occurring on different catalytic sites. The alcohol undergoes oxidation to the corresponding aldehyde with the simultaneous formation of a metal hydride; then, the aldehyde reacts with a nucleophile formed "*in situ*" to give an alkene, and finally, the hydrogen from the hydride is transferred to the alkene to give a new C–C bond.

A kinetic study on the α-monoalkylation reaction of benzylacetonitrile with benzyl alcohol reveals that the rate-controlling step for the one-pot reaction sequence is the hydrogen transfer reaction from the surface hydrides to the olefin, and consequently, the global reaction rate is improved when decreasing the size of the Pd metal particle.

1. Introduction

Reactions directing to the formation of C–C bonds are of much interest in synthetic organic chemistry. Among them, the Knoevenagel condensation affords α–β conjugated enones through the nucleophilic addition of active methylene compounds to carbonyl groups, followed by elimination of a molecule of water. For the Knoevenagel reaction, basic catalysts abstract a proton from the activated methylenic group and form the intermediate carbanion (nucleophile) that will react with the carbonyl group to give the olefin. The double bond can be further hydrogenated in a subsequent step to give a saturated compound.

The two reaction steps previously described (Knoevenagel condensation and hydrogenation) can be carried out in one-pot reaction by means of bifunctional metal–base solid catalysts, while working in the presence of hydrogen [1]. However, there is another way to achieve the final hydrogenated product without the need of added hydrogen. This will consist of a one-pot reaction between an alcohol and a molecule having an activated methylenic group in the presence of a bifunctional metal/base solid catalyst.

In this case, the global process involves in the first step an alcohol which is dehydrogenated on the metal function to yield the corresponding aldehyde (or ketone) and a metal hydride. Meanwhile, the basic function of the catalyst will abstract a proton from the activated methylenic group of the second reactant to give the corresponding carbanion. Both the carbanion and the carbonyl compound will react to give an olefinic condensation product and, finally, the metal hydride will transfer the hydrogen to the double bond to give the final saturated product (see Scheme 1).

This sequential process is based on hydrogen transfer from an alcohol that will act as the hydrogen source [2–9] and may also have interesting and useful applications when the intermediate carbonyl compound is unstable, since it will react *in situ*, and its isolation and purification will not be necessary. Moreover, the process described above can be a convenient procedure especially when a chemoselective hydrogenation of the double bond is required [9b,c].

Typical homogeneous catalysts such as Ru-, Rh-, and Ir-based complexes in d^6 and d^8 electronic configuration are recognized to be most efficient catalysts for transfer hydrogenation while, with the exception of Os, other second or third row elements seem to be much less suited for this catalysis [10–12]. In general, transfer hydrogenation with the above metal complexes involves the use of an alcohol that will serve as hydrogen source with the aid of a metal catalyst, and an alkaline agent that is necessary to activate the C–H bond through formation of the alkoxide ion.

Here, we report the formation of C–C bonds starting from an alcohol, by α-monoalkylation reactions using a Pd–MgO bifunctional catalyst. In this case, the metal will perform a dehydrogenation to give the intermediate carbonyl compound and a palladium dihydride [13]. Then, the reaction of the carbonyl with a variety of

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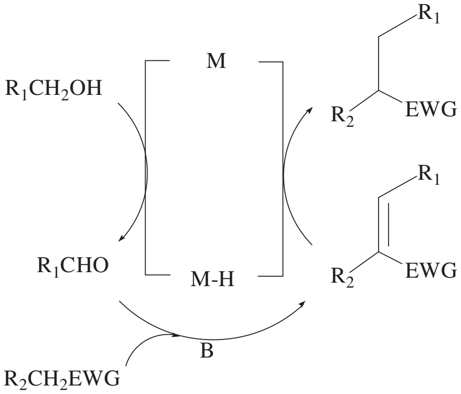

Scheme 1. One-pot α-monoalkylation reaction of methylene compounds with alcohols in the presence of a bifunctional metal–base catalyst (EWG = electron withdrawing group).

methylene compounds with different p*K*s will produce the olefinic condensed products. Finally, the olefins will be hydrogenated to provide the corresponding C–C bond. In this process, which can be considered an extension of the Wittig reaction (well-known method for the conversion of aldehydes into alkenes), an alcohol will serve dually as hydrogen donor and as precursor to the carbonyl electrophile, avoiding the use of homogeneous toxic alkylating agents as well as the formation of dialkylated products.

2. Experimental

Hydroxyapatite (HAP) and hydrotalcite (HT) were prepared following reported procedures [14,15]. A MgO sample with a surface area of 670 m^2/g was purchased from NanoScale Materials. Inorganic salts $Pd(acac)_2$, $NaAuCl_4$, $KAuCN_4$, and $AuPPh_3Cl$ were purchased from Aldrich and $Pt(acac)_2$ was from Acros. The reactants were used without further purification.

2.1. Preparation of catalysts

2.1.1. Preparation of metal (M)–MgO (M = Pd, Pt, Au) bifunctional catalysts

Pd–MgO (0.8 wt.% palladium) was prepared following the procedure reported in [13].

Pt–MgO (1 wt.% metal loading) was obtained by adding 1 g of MgO (670 m^2/g) to 30 ml anhydrous dichloromethane solution containing $Pt(acac)_2$ (24.01 mg, mmol) under stirring for 12 h. After evaporation of the solvent at reduced pressure, the resultant solid was dried overnight at 353 K in vacuum and then calcined in nitrogen flow at 823 K (heating rate: 5 °C/min) for 3.5 h. The sample was activated before reaction by heating the solid at 723 K under air atmosphere for 5 h and then for 5 h under nitrogen. Metal reduction was performed by heating the solid at 523 K in a flow of H_2/N_2 (90/10) for 2 h.

Au–MgO (1 wt.% metal loading) was prepared as follows [16]: 1 g of MgO (670 m^2/g) were added to 30 ml of ethanol solution containing $Au(CH_3)_2(acac)$ (17.963 mg, 0.055 mmol) under stirring for 12 h. The solvent was evaporated at reduced pressure, and the solid was dried overnight at 353 K under vacuum and then calcined in nitrogen flow at 823 K (ramp rate: 5 °C/min) for 3.5 h. The sample was activated before reaction by heating the solid at 723 K under air for 5 h and then for 5 h under nitrogen. Metal reduction was performed by heating the solid at 523 K in a flow of H_2/N_2 (90/10) for 2 h.

Pd–HAP and Pd–HT were prepared according to previous reported procedures [14,15].

2.2. Catalytic tests

2.2.1. α-Monoalkylation of phenylacetonitrile with benzyl alcohol on metal–MgO as catalysts

A mixture of benzyl alcohol (1 mmol), phenylacetonitrile (3 mmol), 0.0998 g of metal–MgO (Pd: 0.0075 mmol; Au: 0.0075 mmol; Pt: 0.0075 mmol), trifluorotoluene (1 ml) and *n*-dodecane (20 μl) as internal standard were placed into an autoclave. The resulting mixtures were vigorously stirred at 180 °C under nitrogen, being monitored by GC.

2.2.2. Catalyzed α-monoalkylation of malonate diester with benzyl alcohol

A mixture of benzyl alcohol (1 mmol), diethylmalonate (3 mmol), 0.0998 g of Pd–MgO (Pd: 0.0075 mmol), trifluorotoluene (1 ml), and *n*-dodecane (20 μl) as internal standard were placed into an autoclave. The resulting mixture was vigorously stirred at 180 °C (or 100 °C) under nitrogen. The reaction was monitored by GC.

2.2.3. Catalyzed α-monoalkylation of nitromethane with benzyl alcohol

Given that oxidation of benzyl alcohol did not occur in the presence of nitromethane (probably due to a strong competitive adsorption of the last molecule on the metal active sites), in this case, the one-pot synthesis was performed in such a way that nitromethane was incorporated when practically all benzyl alcohol was dehydrogenated as follows:

A mixture of benzyl alcohol (1 mmol), 0.0998 g of Pd–MgO (Pd: 0.0075 mmol), trifluorotoluene (1 ml), and *n*-dodecane (20 μl) as internal standard were placed into an autoclave. The resulting mixture was vigorously stirred at 180 °C under nitrogen being monitored by GC. After completing the alcohol transformation to benzaldehyde, nitromethane (3 mmol) was added, and the resulting mixture was vigorously stirred at 180 °C.

3. Results and discussion

The reactivity of Pd on different basic supports such as MgO, Al–Mg hydrotalcite (HT), and hydroxyapatite (HAP) was studied for the α-monoalkylation of phenylacetonitrile with benzyl alcohol as model reaction. 2,3-Diphenylacrylonitrile (**1**) and 2,3-diphenylpropionitrile (**2**), together with small amounts of benzene and toluene, were obtained as reaction products. Better yields of the desired final product (**2**) were obtained with Pd on MgO than on HT or HAP (see entries 1–3, Table 1).

In fact when Pd was supported on Al–Mg hydrotalcite (HT), the resultant catalyst was active but the yield and selectivity to **2** and even **1 + 2** were lower than with MgO. The situation was even worst with HAP, since in this case the basicity was too weak and the catalyst was inactive (see entries 1–3, Table 1). Therefore, on the bases of the results obtained, MgO was selected as the basic component of the bifunctional catalyst.

Fig. 1 shows the evolution with time of the different products obtained when benzyl alcohol and phenylacetonitrile were reacted in the presence of the bifunctional Pd–MgO catalyst.

A priori, formation of the alkene 2,3-diphenylacrylonitrile **1** and 2,3-diphenylpropionitrile **2** can be explained *via* oxidative removal of hydrogen from benzyl alcohol to afford benzaldehyde (not detected by gas chromatography in the presence of the arylnitrile) and a characteristic palladium dihydride intermediate (see Scheme 2) [13,17]. Then, in the presence of the solid base MgO, phenylacetonitrile is activated to give a nucleophile which will rapidly condense with benzaldehyde to give the condensation product **1**, which is hydrogenated by the metal hydride yielding the α-monoalkylated product **2** according to Scheme 2.