

Synthesis of arylacetic acid derivatives from mandelic acid derivatives by hydrogen transfer from H₂O–CO catalyzed by a Pd/C–HCl system

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Received 24 January 1995; accepted 28 March 1995

Abstract

A Pd/C–HCl catalytic system is highly active and selective in the hydrogen transfer from H₂O–CO to ArCHOHCOOH for the synthesis of ArCH₂COOH (Ar is *para* substituted with a OH group). Typical reaction conditions are: temperature 50–70°C; P_{CO} 20–80 atm; solvent: acetonitrile; substrate/Pd/HCl/H₂O = 200–400/1/25–100/500–2000; [Pd] = 0.6–1.2 mmol · l⁻¹. The reaction rate is approximately of the first order with respect to ArCHOHCOOH. The yield increases with the increasing of P_{CO} and of the temperature, as expected, and passes through a maximum with the increasing of the concentration of H₂O and of HCl. The proposed catalytic cycle proceeds through the following steps. (i) H₂O and CO interact with the metal giving rise to an intermediate having a Pd–COOH moiety, which, upon β -hydride abstraction, gives off CO₂ with formation of a Pd–H species. (ii) The starting substrate is in equilibrium, in the presence of HCl, with the corresponding chloride ArCHClCOOH, which adds to the metal forming an intermediate having a Pd–CH(Ar)COOH moiety. (iii) This species interacts with the hydride yielding the product ArCH₂COOH and regenerating the catalyst. The reaction is compared to the closely related catalyzed water gas shift reaction.

Keywords: Carbon dioxide; Carboxylic acids; Hydrochloric acid; Hydrogen transfer; Palladium; Water

1. Introduction

Recently, we have reported a new synthesis of arylacetic acid derivatives by treating the corresponding mandelic acid derivatives with CO, in the presence of a Pd–HCl catalytic system. It was proposed that the catalytic cycle begins with the oxidative addition to a Pd(0) species of the chloride ArCHClCOOR (R = H, Et; the reaction was carried out in an EtOH–benzene medium), that forms in situ by substitution of the α -hydroxy

group of ArCHOHCOOR upon reaction with HCl with formation of an intermediate having a Pd–[CH(Ar)COOR] moiety, which inserts CO into the Pd–C bond to give an intermediate having a Pd–[COCH(Ar)COOR] moiety. Nucleophilic attack of ROH on the carbon atom of the carbonyl group bonded to palladium gives a malonic acid derivative ArCH(COOR)₂, which, upon decarboxylation, yields the final product ArCH₂COOR. It was also proposed that the product can form by protonolysis of the intermediate arising from the oxidative addition step, with concomitant forma-

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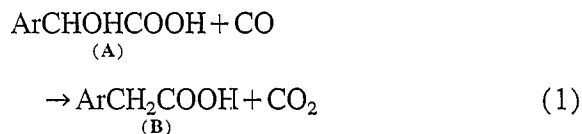
tion of a Pd(II) species, which is reduced by CO to Pd(0), ready to start another catalytic cycle [1].

More recently, we have reported the synthesis of γ -keto acids of the type $\text{PhCOCH}_2\text{CH}_2\text{COOH}$ by treating a β -benzoylacrylic acid $\text{PhCOCH}=\text{CHCOOH}$ (or its reaction products with HCl or H_2O , $\text{ArCOCH}_2\text{CHXCOOH}$ [$\text{X} = \text{Cl}, \text{OH}$]) with CO in the presence of a Pd–HCl catalytic system [2]. The reaction occurs in high yield only in the presence of H_2O . As a matter of fact it has been described as the result of hydrogen transfer from H_2O –CO to the C=C double bond through the following proposed mechanism. The first step is closely related to the first step proposed for the reaction of ArCHOHCOOH to ArCH_2COOH just described: the chloride $\text{PhCOCH}_2\text{CHClCOOH}$, formed in situ upon addition of HCl to the C=C double bond, oxidatively adds to ‘reduced palladium’, with formation of a catalytic intermediate having a Pd–[CH(COOH)CH₂COPh] moiety. ‘Reduced palladium’ is the metal coordinated by other atoms of palladium, and/or by carbon monoxide. Interaction of H_2O and CO on the metal center of this species gives an intermediate having also a carbohydroxy ligand, (HOOC)–Pd–[CH(COOH)CH₂COPh]. β -Hydride abstraction from the carbohydroxy ligand gives a hydride, H–Pd–[CH(COOH)CH₂COPh], with evolution of CO_2 . Finally, reductive elimination of the product $\text{PhCOCH}_2\text{CH}_2\text{COOH}$ returns the catalyst to the catalytic cycle. Alternatively, also for this reaction, it has been proposed that protonolysis of the intermediate that forms in the oxidative addition step yields the product, and, again that the resulting Pd(II) species is then reduced by CO in the presence of H_2O .

Very recently, we have found that the reduction of mandelic acid derivatives to arylacetic acid derivatives by CO, catalyzed by a Pd/C–HCl system, is significantly influenced by the presence of H_2O . The results are described and discussed hereafter, together with the effect of the concentration of HCl and of other reaction parameters, such as temperature, pressure and concentration of the substrate.

2. Results and discussion

The reaction can be schematized as follows:



Previous studies have shown that the reaction occurs in high yield when the aromatic ring is substituted with a hydroxy group in *para* position [1]. All the results reported here refer to the substrate with $\text{Ar} = 4\text{-HO-3-CH}_3\text{OC}_6\text{H}_3$, using Pd/C as catalyst. Even though H_2O does not appear in Eq. (1), the reaction occurs in high yield only in the presence of a suitable amount of H_2O . It is necessary also to add HCl in order to obtain the product in high yield. Typical reaction conditions are: temperature 50–70°C; P_{CO} 20–80 atm; solvent: acetonitrile; substrate/Pd/HCl/ $\text{H}_2\text{O} = 200\text{--}400/1/25\text{--}100/500\text{--}2000$; $[\text{Pd}] = 0.6\text{--}1.2 \text{ mmol} \cdot \text{l}^{-1}$.

The effect of P_{CO} and of the temperature are shown in Fig. 1 and Fig. 2. As expected, the yield increases with increasing the pressure and the temperature.

Fig. 3 shows that the reaction is practically first order with respect to substrate.

Under the conditions reported in Fig. 4 the reaction goes to completeness in ca. 4 h.

As already mentioned, H_2O strongly affects the reaction. In the absence of added H_2O the yield is

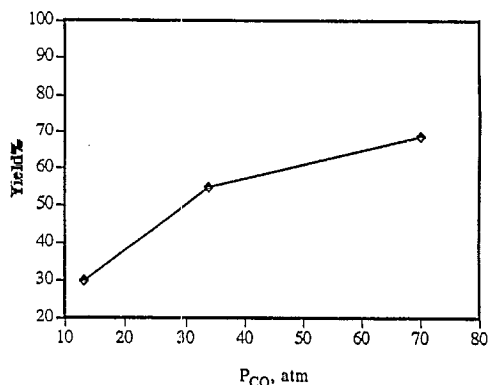


Fig. 1. Run conditions: ArCHOHCOOH 2.5 mmol; 10% Pd/C 6.5 mg, $6 \cdot 10^{-3}$ mmol of Pd; H_2O 16.6 mmol; HCl 2.2 mmol, solvent CH_3CN , 10 ml total volume; 70°C, 2 h.

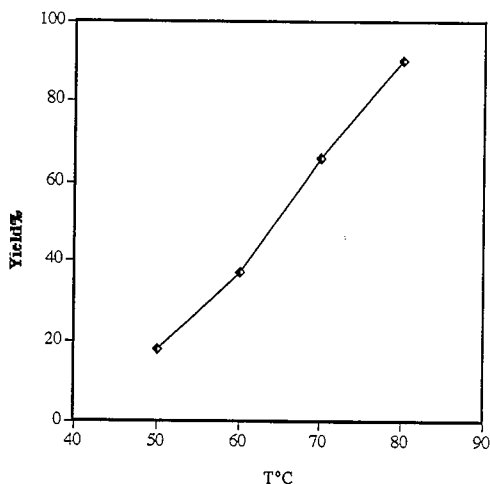


Fig. 2. Run conditions: ArCHOHCOOH 2.5 mmol; 10% Pd/C 6.5 mg, $6 \cdot 10^{-3}$ mmol of Pd; H₂O 11.1 mmol; HCl 4 mmol; P_{CO} 70 atm; solvent CH₃CN, 10 ml total volume, 2 h.

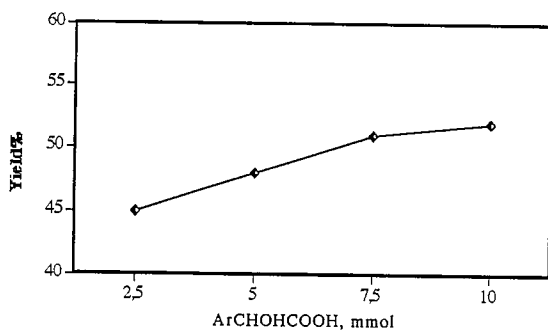
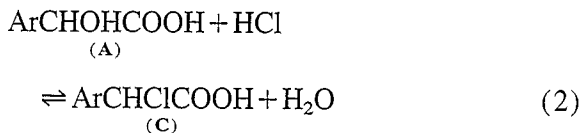


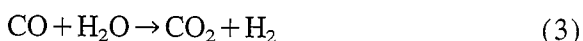
Fig. 3. Run conditions: 10% Pd/C 6.5 mg, $6 \cdot 10^{-3}$ mmol of Pd; H₂O 11.1 mmol; HCl 1.6 mmol; P_{CO} 70 atm; solvent CH₃CN, 10 ml total volume; 70°C, 2 h.

rather low. Under these conditions some water is present because of the equilibrium:



The yield passes through a maximum when the molar ratio water/substrate is ca. 6 and then decreases at higher concentrations of water. This trend suggests that H₂O competes with other reacting molecules for coordination to the metal center.

In practice, reaction (1) occurs with substitution of the α -OH group with a hydride which is proposed (see later) to originate from a mechanism closely related to that responsible for the catalytic water gas shift reaction (WGSR):



Complexes of palladium with phosphine ligands are known to promote the WGSR in 20% aqueous trifluoroacetic acid [3]. The same complexes, under similar conditions (1 atm, 70°C) catalyze the synthesis of diketones from an olefin, CO and water [4]. Quite interestingly, the dependence of the rate of formation of the diketone upon the concentration of H₂O is similar to that shown in Fig. 5. It was proposed that a key step of the reaction is the insertion of the olefin into a Pd-H which forms by proton addition to a Pd(0) species which originates from the reduction of Pd(II) by CO.

In the present case, Pd/C does not promote the WGSR to a significant extent, however for the success of reaction (1) it is not necessary that the hydrogen evolution takes really place, rather

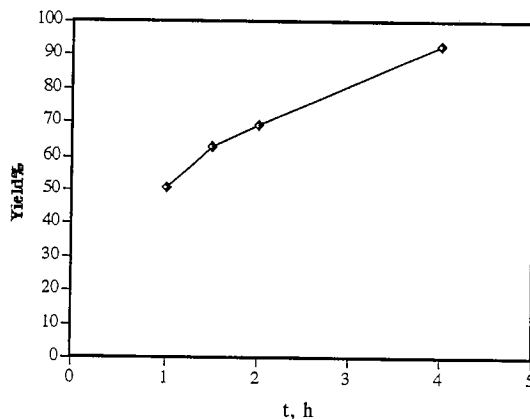


Fig. 4. Run conditions: ArCHOHCOOH 2.5 mmol; 10% Pd/C 6.5 mg, $6 \cdot 10^{-3}$ mmol of Pd; H₂O 16.6 mmol; HCl 2.2 mmol; P_{CO} 70 atm; solvent CH₃CN, 10 ml total volume; 70°C.

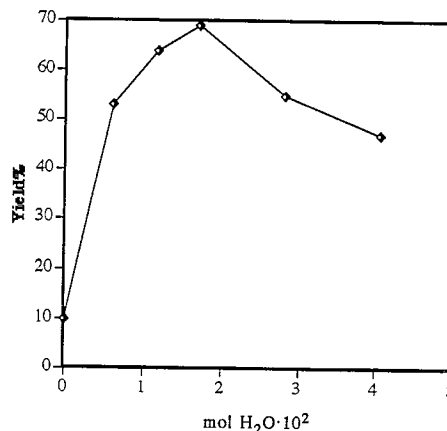
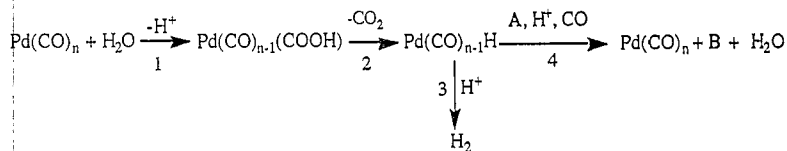


Fig. 5. Run conditions: ArCHOHCOOH 2.5 mmol; 10% Pd/C 6.5 mg, $6 \cdot 10^{-3}$ mmol of Pd; HCl 2.2 mmol; P_{CO} 70 atm; solvent CH₃CN, 10 ml total volume; 70°C, 2 h.



Scheme 1.

being essential that hydrogen is transferred to the substrate. Such a transfer can occur for example via a hydride species as proposed in Scheme 1.

Steps 1–3 are commonly proposed for the catalyzed WGS [5]. Interaction of H_2O with CO on the metal leads to a palladiumcarboxylic acid intermediate, which evolves CO_2 after β -hydride abstraction. This hydride reacts with the proton that forms in the first step with production of molecular hydrogen (step 3). This scheme is also proposed for the catalytic hydrogen transfer from the H_2O – CO system to various organic substrates [6]. In the present case hydrogen evolution is much slower compared to the hydride transfer to (A), so that product (B) can be obtained in high yield without formation of molecular hydrogen.

Reaction (1) occurs in high yield only in the presence also of HCl , in addition to H_2O . The effect of the concentration of hydrochloric acid is shown in Fig. 6. The yield at first increases upon increasing the concentration of the acid, passes through a maximum and then decreases.

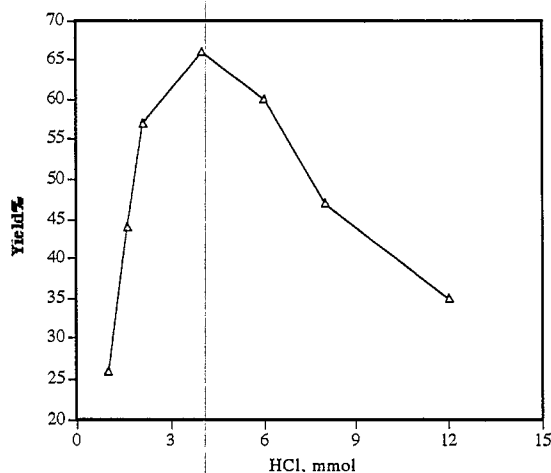
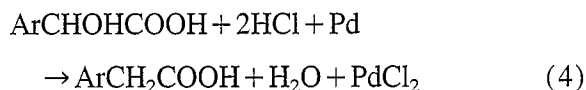


Fig. 6. Run conditions: ArCHOHCOOH 2.5 mmol; 10% Pd/C 6.5 mg, $6 \cdot 10^{-3}$ mmol of Pd; H_2O 11.1; P_{CO} 70 atm; solvent CH_3CN , 10 ml total volume; 70°C , 2 h.

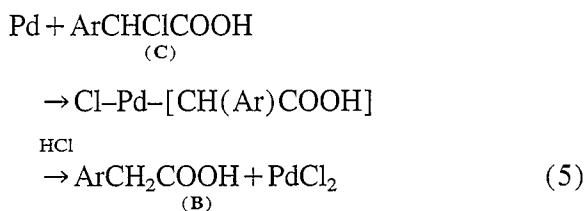
It should be underlined that, as already pointed out, reaction (1) occurs in high yield only when the substrate is *para* substituted with an OH group. For example mandelic acid does not yield any phenylacetic acid. A reasonable rationalization of this drastic difference in the reactivity, which must be associated with the nature of the substituent, is the following. Reaction (1) occurs with formation of an $\alpha\text{-C-H}$ bond at the expense of an $\alpha\text{-C-OH}$ bond. Protonation of this OH group, by HCl , makes it a better leaving group, thus favoring the substitution process, which is further facilitated when the incipient positive charge on the $\alpha\text{-C}$ can be delocalized through the OH substituent in the *para* position. The substitution process may involve the intermediacy of a species having a Pd–[CH(Ar)COOR] moiety (see later, Scheme 2), which can form by addition of chloride (C) to palladium. The oxidative addition of organic halides, such as aryl, benzyl, styryl, vinyl and allyl halides, to finely divided low valent nucleophilic palladium metal has been widely proposed in many different catalytic reactions [7–12].

The trend shown in Fig. 5 may be the result of two opposite effects. On the one hand on increasing the concentration of H_2O the hydrogen transfer is favored, however the substitution process may be partially inhibited. The trends of Fig. 5 and of Fig. 6 suggest also that HCl and H_2O compete for the coordination to the metal center. As a matter of fact, it is well known that HCl adds to $\text{Pd}(0)$ complexes to give a chloride of $\text{Pd}(II)$ with concomitant evolution of hydrogen [13]. Moreover, the addition of HCl to palladium metal has been proposed for example in the catalytic carbonylation of olefins to acids in the presence of water [14]. Thus, while the formation of a species having a palladiumcarboxylic acid moiety Pd–(COOH) might play a key role in the evolution

of CO₂, the hydrogen transfer that yields product (**B**) may occur through a route different from that proposed in Scheme 1. In order to gain some insight into the role of the Pd–HCl system in the hydrogen transfer to ArCHOHCOOH, we attempted the stoichiometric synthesis of ArCH₂COOH by contacting, in the absence of CO, ArCHOHCOOH with HCl and palladium in equivalent amounts according to the stoichiometry of the reaction:

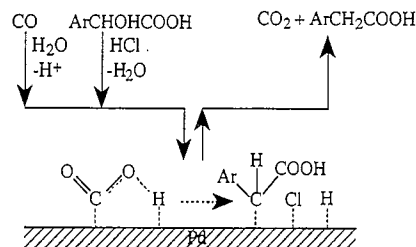


At 70–100°C, under nitrogen atmosphere, in acetonitrile as solvent, there is no formation of ArCH₂COOH. This result also proves that product (**B**) does not form by protonolysis of a possible intermediate having a Pd–[CH(Ar)COOH] moiety:



These observations do not completely exclude that the palladium carbonyls, which are likely to form in the presence of CO under catalytic conditions, can promote reactions (4) or (5), with a difference of palladium metal. If this is the case, the resulting Pd(II) species that forms is then reduced to palladium metal by CO in the presence of H₂O to allow catalysis to proceed. Under these conditions, even though HCl is not strictly necessary in order to form a hydridic species because this can also form via β-hydride extraction from Pd–COOH, nevertheless the acid may play a beneficial role by increasing the concentration of a hydridic species and/or by yielding a more reactive hydride when the metal center is also coordinated by some chloride ligands.

On the basis of these observations, the catalytic process is proposed to occur as depicted in Scheme 2.

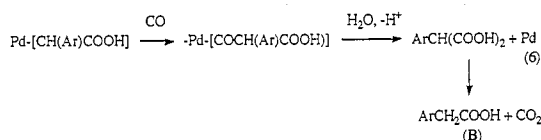


Scheme 2. Proposed reaction pathway for the hydrogen transfer from H₂O–CO to ArCHOHCOOH.

The essential features of the catalytic cycle are the following. (i) H₂O and CO interacts with the metal giving rise to an intermediate having a Pd–COOH moiety, which, upon β-hydride abstraction, gives off CO₂ with formation of a Pd–H species (eventually the proton generated in this step interacts with the metal or gives an oxonium ion). (ii) The starting substrate is in equilibrium, in the presence of HCl, with the corresponding chloride ArCHClCOOH, which adds to the metal forming an intermediate having a Pd–CH(Ar)COOH moiety (in this step HCl is likely to compete with the organic chloride for the activation to the metal). (iii) This species interacts with the hydride yielding the product, ArCH₂COOH.

Product (**B**) could form also via CO insertion into a Pd–[CH(Ar)COOH] intermediate, followed by nucleophilic attack of H₂O to form a malonic acid product intermediate ArCH(COOH)₂, which, upon decarboxylation, yields (**B**) as depicted in Scheme 3.

In order to verify this possibility we carried out a catalytic reaction at relatively low temperature (30–40°C), till a low though significant amount of (**B**) was produced. Under these mild conditions the malonic acid derivative is stable, but it has not been detected in the reaction medium. This result excludes that product (**B**) forms through a malonic acid route.



Scheme 3. Proposed reaction pathway for the hydrogen transfer from H₂O–CO to ArCHOHCOOH.

3. Experimental

3.1. Materials

Carbon monoxide was purchased from S.I.O. Company. Solvents were HPLC grade. α -4-dihydroxy-3-methoxybenzeneacetic acid was prepared as described in the literature [15]. The catalyst 10% Pd/C, type Escat 11, was a gift of the Engelhard Company.

3.2. Product identification and analysis

Products were identified and analyzed by IR, using a Perkin Elmer spectrometer model 683, by NMR, on a Varian FT 80 A instrument, and by HPLC, on a Perkin Elmer liquid chromatograph, model HPLC series 10 using a C18-SIL-X-10 column of 25 cm, solvent: H₂O 70%, CH₃CN 30% containing 2% CH₃COOH.

3.3. Catalytic synthesis of ArCH₂COOH (Ar = 4-HO-3-CH₃OC₆H₃) by hydrogen transfer from H₂O–CO to ArCHOHCOOH catalyzed by Pd/C in the presence of HCl

The reactions were carried out in a stainless steel autoclave of ca. 70 ml. The catalyst, reagent and solvent were contained in a Pyrex bottle placed in the autoclave. A magnetic stirrer was provided to stir the reaction medium.

In a typical experiment, 6.5 mg of 10% Pd/C catalyst ($6 \cdot 10^{-3}$ mmol of Pd), 2.5 mmol of ArCHOHCOOH, solvent CH₃CN together with the desired amount of H₂O and of HCl (total volume 10 ml) were employed. The autoclave was purged with carbon monoxide at room temperature and then charged with the same gas at the desired pressure. The autoclave was placed in a heated oil bath. The working temperature, typically 50–70°C, was reached in ca. 10 min and maintained throughout the experiment (2 h). The autoclave was then cooled in an ice bath and slowly depressurized. The reaction solution was analyzed by HPLC.

3.4. Attempted synthesis of ArCH₂COOH from ArCHOHCOOH, palladium and HCl in the absence of CO

ArCHOHCOOH (2.5 mmol), aqueous 37% HCl (5 mmol of HCl), and 2.7 g of 10% Pd/C (2.5 mmol of palladium) were heated at 70°C for 2 h, in an autoclave previously purged with nitrogen. After cooling the reaction mixture, analyzed by HPLC, did not show the presence of ArCH₂COOH.

Acknowledgements

The authors thank the National Research Council (C.N.R.) for sponsoring this research (Progetto Strategico) and the Engelhard Company of Milan for generous gift of palladium catalyst.

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