

Reprinted from

JOURNAL OF MOLECULAR CATALYSIS

Journal of Molecular Catalysis 89 (1994) 93–100

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(Received August 19, 1993; accepted November 17, 1993)





Synthesis of γ -ketocarboxylic acids via reduction of γ -keto- α -hydroxycarboxylic acids with carbon monoxide catalyzed by a Pd–HCl system

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Abstract

A Pd–HCl catalytic system is highly active in the synthesis of γ -ketoacids of type $\text{ArCOCH}_2\text{CH}_2\text{COOH}$ via reduction with CO of the ketohydroxy acids $\text{ArCOCH}_2\text{CHOHCOOH}$. Typical reaction conditions are: P_{CO} : 20–30 atm; Pd/substrate/ H_2O /HCl = 1/400–1000/800–3000/100–1000 (mol); temperature: 100–110°C; [Pd]: 10^{-3} to 10^{-2} M; solvent: dioxane; reaction time: 1–2 h. The reaction occurs in high yield only when the palladium precursor is used in combination with HCl and in the presence of H_2O . Under the reaction conditions employed, the palladium(II) complex used as catalyst precursor decomposes to palladium metal. Pd/C is also highly active. It is proposed that the catalytic cycle proceeds through the following steps: (i) The chloride $\text{ArCOCH}_2\text{CHClCOOH}$, which forms in situ from the starting substrate and HCl, undergoes oxidative addition to reduced palladium with formation of a catalytic intermediate having a Pd–[CH(COOH)CH₂COPh] moiety. (ii) Interaction of H_2O and CO on the metal yields an intermediate having also a carbohydroxy ligand, (HOOC)–Pd–[CH(COOH)CH₂COPh]. (iii) This intermediate, after β -hydride abstraction from the carbohydroxy ligand, gives off CO_2 and reductive elimination gives product $\text{PhCOCH}_2\text{CH}_2\text{COOH}$. Alternatively, HCl may react with the intermediate proposed in step (i), yielding directly the product and a Pd(II) species, which is reduced by CO to a Pd(0) species, which starts another catalytic cycle.

Key words: carbon monoxide; carboxylic acids; hydrochloric acid; palladium; reduction

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1. Introduction

The increasing interest in the use of carbon monoxide in catalytic organic syntheses is mainly due to the fact that always new applications are found [1]. Among these are the hydrocarbalkoxylation of olefins to esters, which yields also unsaturated esters when properly carried out under oxidative conditions, the single and double carbonylation of alkyl halides, the carbon monoxide–olefin copolymerization to polyketones, the synthesis of alkyl carbonates and of oxalate esters and the reductive carbonylation of nitroaromatics to isocyanates [2–8].

Recently, we studied the carbonylation of α -chlorocarboxylic acid derivatives with the aim of synthesising malonic acid derivatives. Quite interestingly, the reaction of $\text{PhCOCH}_2\text{CHClCOOH}$ with CO, catalyzed by a Pd system, in the presence of water, yielded the unsuspected γ -keto acid $\text{PhCOCH}_2\text{CH}_2\text{COOH}$ with CO_2 evolution [9]. This new catalytic reaction occurs with substitution of the halogen with hydrogen, formally through a carbonylation–decarboxylation reaction. It has been proposed that the catalytic cycle proceeds through the following steps: (i) The chloride $\text{PhCOCH}_2\text{CHClCOOH}$ undergoes oxidative addition to reduced palladium with formation of a catalytic intermediate having a $\text{Pd}-[\text{CH}(\text{COOH})\text{CH}_2\text{COPh}]$ moiety. (ii) Carbon monoxide “inserts” into the $\text{Pd}-\text{C}$ bond of this intermediate to give an acyl catalytic intermediate having a $\text{Pd}-[\text{COCH}(\text{COOH})\text{CH}_2\text{COPh}]$ bond. (iii) Nucleophilic attack of H_2O to the carbon atom of the carbonyl group bonded to the metal of the acyl intermediate yields a malonic acid derivative as product intermediate. This, upon decarboxylation, gives the final product. Alternatively, the acyl intermediate proposed in step (ii) undergoes decarboxylation with formation of a different acyl intermediate $\text{Pd}-(\text{COCH}_2\text{CH}_2\text{COPh})$, which reacts with H_2O yielding the final product.

This reaction is closely related to the synthesis of arylacetic acid derivatives from mandelic acid derivatives and CO, catalyzed by a $\text{Pd}-\text{HCl}$ system, recently also reported by us [10,11]. For this reaction it has been proposed a similar catalytic cycle that begins with the oxidative addition to a $\text{Pd}(0)$ species of the chloride ArCHClCOOH that forms in situ from the reaction of the starting compound ArCHOHCOOH with HCl and that, after CO “insertion” and nucleophilic attack of H_2O , yields a malonic acid derivative which, upon decarboxylation, yields the acetic acid derivative [10]. It has been proposed also that HCl interacts with the intermediate that forms in the oxidative addition step yielding directly the final product and a $\text{Pd}(\text{II})$ species which is reduced by CO to palladium metal, ready for another catalytic cycle [10].

This reaction is equivalent to the hydrogenation of the $\text{C}-\text{Cl}$ bond to a $\text{C}-\text{H}$ bond. The advantage of carrying out the reaction with CO lies in the fact that it is quite selective, whereas when hydrogen is used there is competitive hydrogenation of the aromatic ring to a cyclohexyl ring, with consequent lowering of the selectivity and additional difficulties for the purification of the desired product.

In this paper we extend this new methodology to the reduction with CO of hydroxyketo acids of the type $\text{PhCOCH}_2\text{CHOHCOOH}$ to $\text{PhCOCH}_2\text{CH}_2\text{COOH}$.

2. Results and discussion

γ -Keto- α -hydroxy acids are reduced to the corresponding γ -ketoacids by CO in the presence of catalytic amounts of a palladium(II) precursor and of HCl and H₂O, the last two components in amounts comparable to that of the substrate. In the absence of HCl and of H₂O the product forms in poor yield. The reaction can be schematized as follows:



Typical reaction conditions are: P_{CO} : 20–30 atm; Pd/substrate/H₂O/HCl = 1/400–1000/800–3000/100–1000 (mol); temperature: 100–110°C; [Pd]: 10⁻³ to 10⁻² M; solvent: dioxane; reaction time: 1–2 h.

Under the above reaction conditions, the catalytic precursors listed in Table 1 decompose to palladium metal. The extent of the decomposition depends on the reaction conditions. Qualitative observations show that PdCl₂(PPh₃)₂ is less stable at higher temperature, higher concentration of HCl and of H₂O, and lower concentration of the precursor and of PPh₃. These findings, together with the fact that in the presence of additional amounts of PPh₃, and in the absence of HCl and of H₂O, PdCl₂(PPh₃)₂ does not decompose to metallic palladium [12], suggest that the reduction is likely to take place through displacement of PPh₃ by HCl, followed by reduction to Pd(0) by CO, which is oxidized to CO₂ in the presence of water. The reduction is schematized below:

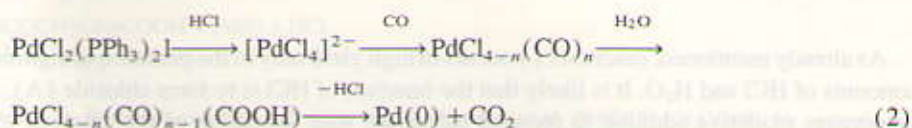


Table 1

Synthesis^a of PhCOCH₂CH₂COOH by reduction of PhCOCH₂CHOHCOOH with CO catalyzed by different catalyst precursors

Run No.	Catalyst precursor	Yield (%)
1	Pd(PPh ₃) ₄	96
2	PdCl ₂	96
3	PdCl ₂ , PPh ₃ ^b	95
4	[PdCl ₂ (PPh ₃) ₂]	97
5	PdCl ₂ (PPh ₃) ₂	97
6	Pd(AcO) ₂	98
7	Pd(AcO) ₂ , PPh ₃ ^b	97
8	[PdCl(1,3- η -C ₅ H ₅) ₂]	98
9	[PdCl(1,3- η -C ₅ H ₅) ₂], PPh ₃ ^b	97
10	10% Pd/C	98
11	Pd/C, PPh ₃ ^b	97

^aRun conditions: [Pd] = 2 · 10⁻³ M; Pd/substrate/HCl/H₂O = 1/550/440/1500; solvent: dioxane; P_{CO} = 30 atm at room temperature; temperature: 110°C; reaction time: 2 h.

^bPd/P = 1/2.

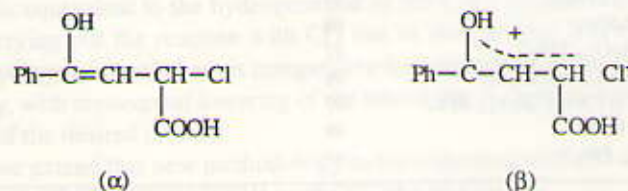
As a matter of fact, it has been reported that, under strictly anhydrous conditions, in the presence of thionyl chloride, PdCl_2 reacts with CO at super atmospheric pressure (50–80 atm), at 120°C, to give the dimer $\text{Pd}_2\text{Cl}_4(\text{CO})_2$, which quickly decomposes to a black precipitate, presumably palladium metal, upon contact with water [13]. It has also been found that the dimer reacts with $\text{NH}_2\text{Et}_2\text{Cl}$ to give $\text{NH}_2\text{Et}_2[\text{PdCl}_3(\text{CO})]$ and with PPh_3 to give the dimer $[\text{Pd}_2\text{Cl}_4(\text{PPh}_3)_2]$ and the monomer $\text{PdCl}_2(\text{PPh}_3)_2$ [13], thus practically reversing reaction (2). The reduction probably occurs via the intermediacy of some chlorocarbonylpalladium(II), that is likely to form through interaction of H_2O with a carbonyl ligand (see later the proposed catalytic cycle).

The precursors employed give practically the same results, as well as Pd/C (run 10 and 11). These findings suggest that the catalytic cycle involves the reduced metal as a key active species. The fact that the catalytic activity is practically the same, irrespective of the nature of the precursor employed, is probably due to the presence of relatively large amounts of HCl that may level off any major possible difference in the catalytic system generated from the different precursors. It is interesting to observe that the catalytic activity is basically the same either in the presence of a ligand such as PPh_3 or in its absence, thus suggesting that this ligand does not play an important role under the reported run conditions. This behaviour has also been found for the closely related reaction of mandelic acid derivatives to arylacetic acid derivatives, catalyzed by Pd–HCl systems [10,11].

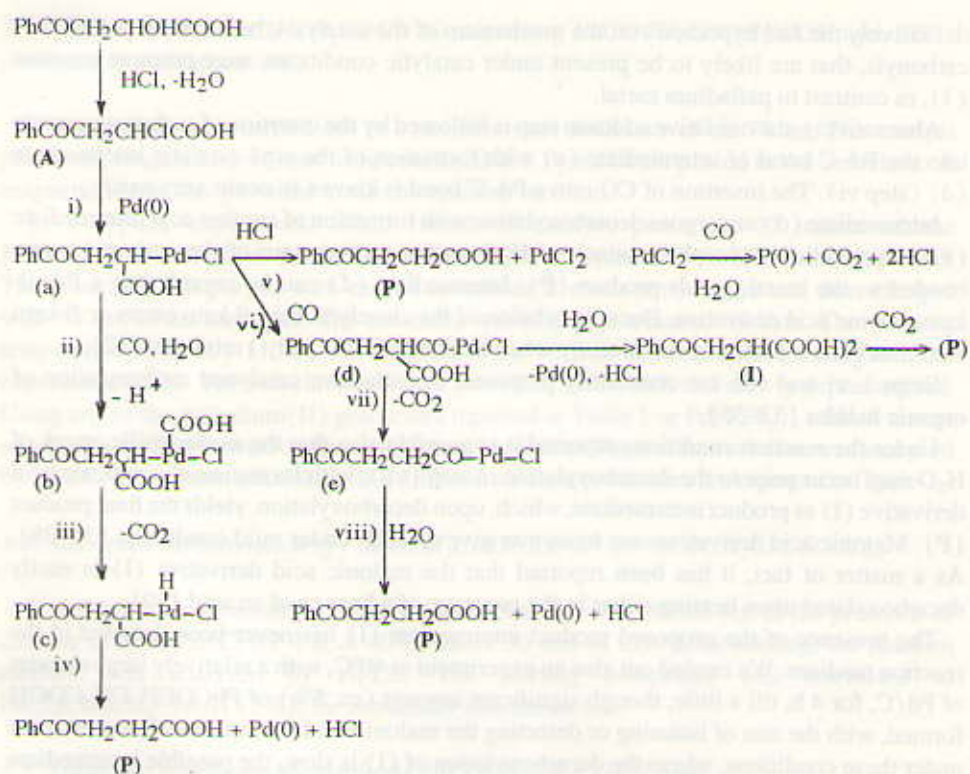
2.1. On the catalytic cycle

As already mentioned, reaction (1) occurs in high yield only in the presence of significant amounts of HCl and H_2O . It is likely that the function of HCl is to form chloride (A), that undergoes oxidative addition to reduced palladium with formation of the catalytic intermediate (a), having a $\text{Pd}-[\text{CH}(\text{COOH})\text{CH}_2\text{COPh}]$ moiety (see Scheme 1). Oxidative addition to reduced palladium is known to occur readily with aryl, benzyl, vinyl, and allyl halides [14–22]. Reduced palladium is the metal coordinated by other atoms of palladium, and/or by carbon monoxide, and/or a PPh_3 ligand, when catalysis is carried out in the presence of this ligand.

An allylic structure of type (α) and a structure of type (β) may contribute to ease the oxidative addition step of the chloride to palladium. As a matter of fact allyl chlorides are known to undergo facile palladium catalyzed carbonylation reactions [17,23–29] and structure (β) favors the nucleophilic attack of palladium to the α -carbon atom in the oxidative addition step.



Relevant to this, for the carbonylation of the γ -ketochloride $\text{CH}_3\text{COCH}_2\text{CH}_2\text{Cl}$ to levulinic acid $\text{CH}_3\text{COCH}_2\text{CH}_2\text{COOH}$, catalyzed by a palladium system, structures of type (α)

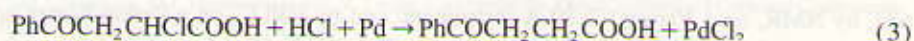


Scheme 1. Proposed catalytic pathways for the synthesis of $\text{PhCOCH}_2\text{CH}_2\text{COOH}$ by reduction of $\text{PhCOCH}_2\text{CHOHCOOH}$ with CO.

and (β) have also been proposed in order to account for the high catalytic activity observed, comparable to that of the systems here reported [30].

In step (ii), interaction of H_2O and CO on the metal yields intermediate (b) having also a carbohydroxy ligand. This intermediate, after β -hydride abstraction from the carbohydroxy ligand, gives off CO_2 (step iii) [31] and yields reductive elimination of product (P) (step iv).

It is also possible that, after the oxidative addition step (i), HCl (or the Pd-hydride-chloride that is likely to form on the surface of the metal) may react with the catalytic intermediate (a), yielding directly the final product (step v), without any decarboxylation process, and a Pd(II) species which is reduced by CO to Pd(0), ready for another catalytic cycle. In order to support this possibility, the starting substrate was treated with an equimolecular amount of aqueous HCl in dioxane, in the presence of a stoichiometric amount of Pd/C, at 110°C , under nitrogen atmosphere and in the absence of CO. In principle, under these conditions, the keto-chloride that forms in situ, could undergo the following reaction:



However, the γ -keto acid $\text{PhCOCH}_2\text{CH}_2\text{COOH}$ did not form. This does not exclude

definitively the last hypothesis on the mechanism of the catalysis, because the palladium-carbonyls, that are likely to be present under catalytic conditions, may promote reaction (3), in contrast to palladium metal.

Alternatively, the oxidative addition step is followed by the insertion of carbon monoxide into the Pd–C bond of intermediate (a) with formation of the acyl catalytic intermediate (d) (step vi). The insertion of CO into a Pd–C bond is known to occur very easily.

Intermediate (d) undergoes decarboxylation with formation of another acyl intermediate (e), which, after nucleophilic attack of H₂O on the carbon atom of the carbonyl group bonded to the metal, yields product (P). Intermediate (d) can be regarded as a Pd- β -ketomalonic acid derivative. Decarboxylation of the closely related β -keto esters or β -keto acids has been reported to occur easily when heated in DMSO–H₂O mixtures [32].

Steps i, vi and viii are commonly proposed in palladium catalyzed carbonylation of organic halides [33–35].

Under the reaction conditions reported it is possible also that the nucleophilic attack of H₂O may occur prior to the decarboxylation in step (vii), with formation of a malonic acid derivative (I) as product intermediate, which, upon decarboxylation, yields the final product (P). Malonic acid derivatives are known to give off CO₂ under mild conditions [36–38]. As a matter of fact, it has been reported that the malonic acid derivative (I) is easily decarboxylated upon heating either in the presence of a base or of an acid [39].

The presence of the proposed product intermediate (I) has never been detected in the reaction medium. We carried out also an experiment at 40°C, with a relatively large amount of Pd/C, for 4 h, till a little, though significant amount (ca. 5%) of PhCOCH₂CH₂COOH formed, with the aim of isolating or detecting the malonic acid derivatives. However, even under these conditions, where the decarboxylation of (I) is slow, the possible intermediate (I) could not be detected, the only other keto derivative present in the reaction medium being the unreacted starting substrate (ca. 95%).

3. Experimental

3.1. Materials

Carbon monoxide, quality N37, was purchased from S.I.O. Company. Solvents were HPLC grade. γ -Oxo- γ -phenyl- α -hydroxypropanoic acid was prepared by reacting acetophenone with glyoxylic acid as described in the literature [39]. The catalyst precursors PdCl₂(PPh₃)₂, [PdCl₂(PPh₃)₂]₂, [PdCl(1,3- η -C₃H₅)₂]₂, Pd(PPh₃)₄ were prepared following known procedures [40–43]. PdCl₂, Pd(OAc)₂, and 10% Pd/C, type Escat 11, were gifts 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. Synthesis of $\text{PhCOCH}_2\text{CH}_2\text{COOH}$ by reaction of $\text{PhCOCH}_2\text{CHOHCOOH}$ with CO catalyzed by palladium–HCl

The reactions were carried out in a stainless steel autoclave of ca. 70 ml. The catalyst precursor, 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, 0.022 mmol of catalyst precursor, 11 mmol of the $\text{PhCOCH}_2\text{CHOHCOOH}$, 8 ml of dioxane, 0.8 ml of aqueous 37% HCl were employed. The autoclave was purged with carbon monoxide at room temperature and then charged with 30 atm of the same gas. The autoclave was placed in a heated oil bath. The working temperature, typically 110°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. Using any of the palladium(II) precursors reported in Table 1 or $\text{Pd}(\text{PPh}_3)_4$ a black mirror of palladium metal formed on the wall of the glass bottle. The reaction solution was analyzed by HPLC. The results obtained using different catalyst precursors are reported in Table 1.

3.4. Attempted carbonylation of $\text{PhCOCH}_2\text{CHOHCOOH}$ to $\text{PhCOCH}_2\text{CH}(\text{COOH})_2$

Following the procedure just described, the reaction was carried out in the presence of 250 mg of 10% Pd/C, for 4 h, at 40°C, under 30 atm of CO. After cooling, the reaction mixture was analyzed by HPLC. The starting compound was converted to $\text{PhCOCH}_2\text{CH}_2\text{COOH}$ (5%), the remainder was unreacted.

3.5. Attempted stoichiometric synthesis $\text{PhCOCH}_2\text{CH}_2\text{COOH}$ from $\text{PhCOCH}_2\text{CHOHCOOH}$, palladium and HCl

The starting compound, dissolved in dioxane, was treated with a stoichiometric amount of 10% Pd/C and of aqueous 37% HCl, at 110°C, under nitrogen atmosphere, for 2 h. After cooling, the reaction mixture showed only the presence of the starting compound and of the corresponding chloride $\text{PhCOCH}_2\text{CHClCOOH}$ (HPLC analysis).

4. Acknowledgements

The authors thank the Italian National Council of Research (C.N.R.) for sponsoring this research (Progetto Finalizzato Chimica Fine II) and the Engelhard Company of Milan for generous gift of catalysts.

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