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CATALYTIC REACTION MECHANISMS

Carbonylation of α-Haloketones

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Abstract—The catalytic carbonylation reactions of α-haloketones in the presence of palladium compounds were studied. Chloroketones were selectively converted into β-ketoesters, whereas bromoacetophenone was partially reduced to acetophenone. The reaction rate at atmospheric pressure was much lower than that at an elevated pressure. A reaction mechanism was proposed.

INTRODUCTION

β-Ketoesters are widely used in technology, organic synthesis, and related fields [1–15]. The condensation of β-ketoesters with nitrogen-containing binucleophiles is the main method of preparing pyridines and pyrazolones [1–7]. β-Ketoesters are used in the synthesis of biologically active compounds and their analogs [3–7]. The preparation of ligands for homogeneous catalysis [8], the synthesis of chelate complexes for supporting metal polarizer microfilms [9–12], the stabilization of polymers [13], the technology of liquid crystals [14], and the preparation of sols and polymers using the sol–gel technology [15] are other areas of the application of β-ketoesters.

Catalytic carbonylation is widely used for introducing carbonyl functional groups into molecules. The carbonylation of aryl halides, allyl halides, benzyl halides, vinyl halides, alcohols, olefins, and alkynes to the corresponding aldehydes, ketones, carboxylic acids, and their derivatives was studied in detail [16–19].

On the other hand, published data on the carbonylation of α-haloketones on palladium catalysts are scanty. The yields are usually low. The carbonylation of α-bromoacetophenone on $PdCl_2(PPh_3)_2$ in the presence of N^1,N^1,N^8,N^8-tetramethyl-1,8-naphthalenediamine at 350 K and 1.3 MPa was performed. The yield of methyl benzoylacetate was 64% in 48 h [20]. The ethyl [21] and *tert*-butyl [22] esters of benzoylacetic acid were obtained by the carbonylation of α-chloroacetophenone on the phosphinic and phosphonic complexes of palladium in 25–50% yields. Cavinato and Toniolo [23] reported the results of the ethoxycarbonylation of 2-chlorocyclohexyl ketone to the corresponding β-ketoester on $PdCl_2(PPh_3)_2$ in the presence of PPh_3. The yield was as high as 80% at 10 MPa; however, it dramatically decreased as the pressure was reduced.

We systematically studied the carbonylation reactions of α-haloketones on palladium catalysts. The effects of the nature of the catalyst, the nucleophile alcohol, and the base, as well as the effects of temperature and pressure on the yields of products were studied. A reaction mechanism was proposed.

EXPERIMENTAL

The parent haloketones were synthesized by the direct halogenation of ketones or by the acylation of arenes with acetyl chloride [24].

Carbonylation reactions at elevated pressures were performed in a steel autoclave equipped with a magnetic stirrer. A substrate (3 mmol), $PdCl_2(PPh_3)_2$ (or $Pd(dba)_2 + 2PPh_3$) (0.03 mmol), Bu_3N (4.5 mmol), and MeOH (10 ml) were placed in the reactor, and the contents were purged with CO several times. When the required reaction temperature was reached, the pressure was adjusted to the required value, and the magnetic stirrer was turned on. After 2 h, the reactor was cooled; the pressure was reduced to atmospheric pressure, and the reaction mixture was removed. The solvent was removed on a rotary evaporator; the residue was washed with 20% HCl (10 ml) and extracted with diethyl ether (three portions of 20 ml). The combined extracts were washed with water to pH 7 and dried with Na_2SO_4; the solvent was removed at a reduced pressure. The product was purified by recrystallization or chromatography. The resulting ketoesters were characterized using ^{1}H NMR and IR spectroscopy and mass spectrometry.

Carbonylation reactions at atmospheric pressure were performed in a thermostatted glass reactor with a heating jacket. The reactor was connected to a graduated burette filled with carbon monoxide. A catalyst, a base, and a solvent were loaded in the reactor; the reactor was purged with CO and thermostatted at the required temperature. Thereafter, a substrate was intro-

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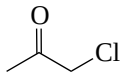
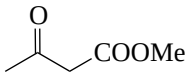
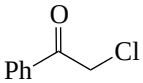
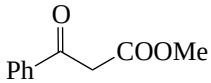
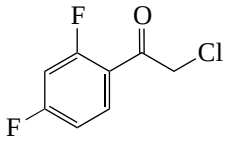
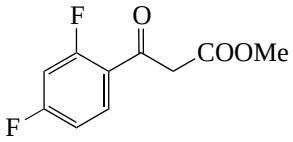
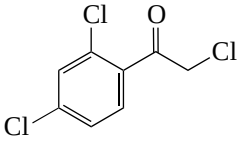
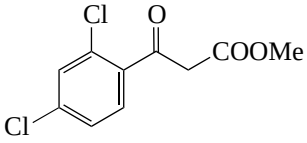
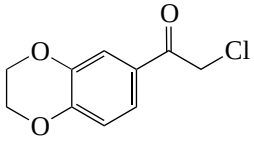
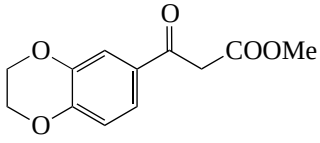
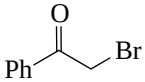
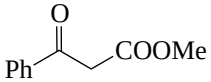
Carbonylation of halomethyl ketones **1** to β-ketoesters **2**. T = 383 K; P = 1.5 MPa; 2 h; $RCOCH_2X + CO + MeOH + Bu_3N \longrightarrow RCOCH_2COOMe + Bu_3NH^+X^-$

Substrate	Product	Yield*, %
1a 	**2a** 	80(98)
1b 	**2b** 	86(95)
1c 	**2c** 	70
1d 	**2d** 	68
1e 	**2e** 	88
1f 	**2b** 	53(60)**

* Preparative yield. Yields calculated from GLC data are given in parentheses.

** Acetophenone (33%) was detected in the reaction mixture.

duced. The course of the reaction was monitored by measuring gas absorption from the burette.

The ^{1}H NMR spectra were measured on a Bruker WM-250 spectrometer; trimethylsilane (TMS) was used as an internal standard. The IR spectra were recorded on a Specord M 80 spectrometer. The mass spectra were measured on a Cratos MS-30 instrument. The reaction mixture was analyzed on an Avtochrom UA5 PID chromatograph with an SE-30 capillary column (30 m × 0.25 mm); helium was the carrier gas, and *n*-octanol was used as an internal standard.

RESULTS AND DISCUSSION

The carbonylation of α-haloketones consists in the replacement of a halogen by a carboxyl group with the formation of a β-ketoester:

$$\underset{\mathbf{1}}{RCOCH_2X} + CO + R'OH + B \longrightarrow \underset{\mathbf{2}}{RCOCH_2COOR'} + BH^+X^-,$$

where R, R' = alkyl, aryl; X = Cl, Br; and B is a base (see the table).

The effect of reaction conditions on the yield of the product was studied with the use of the carbonylation of chloroacetone (**1a**) to methyl acetoacetate (**2a**) as an example. A high yield of the carbonylation product was obtained on $PdCl_2(PPh_3)_2$ at 383 K and 1.5 MPa of CO in the presence of tributylamine as a base. Other palladium compounds free of phosphine ligands, such as $PdCl_2$, $Pd(OAc)_2$, and $PdCl_2(PhCN)_2$, were found inactive. The use of $CaCO_3$, K_2CO_3, or pyridine as a base did not give satisfactory results: only trace amounts of ester **2a** were detected in the reaction mixture. With the use of Na_2CO_3, the yield was 46%.

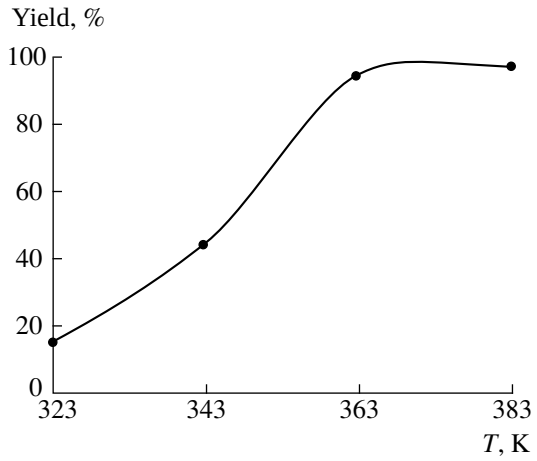


Fig. 1. The temperature dependence of the yield of methyl acetoacetate. P = 1.5 MPa.

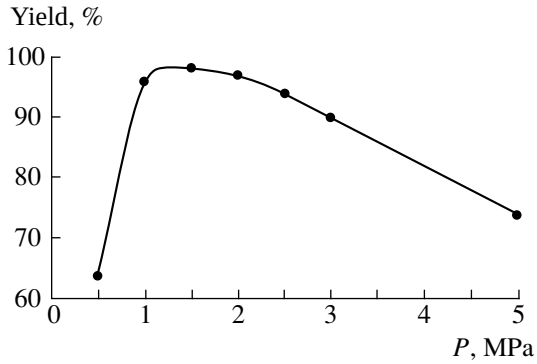


Fig. 2. The pressure dependence of the yield of methyl acetoacetate. T = 383 K.

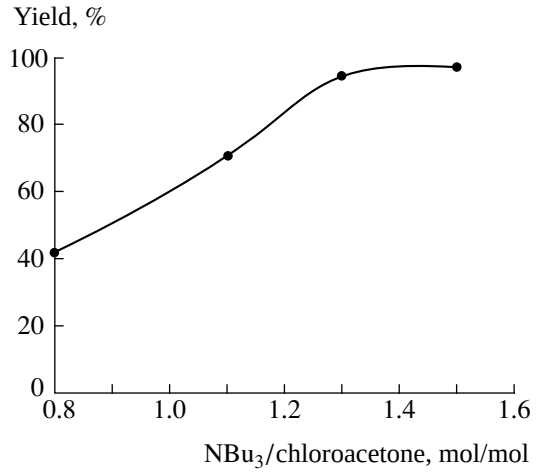


Fig. 3. Dependence of the yield of methyl acetoacetate on tributylamine concentration. T = 383 K; P = 1.5 MPa.

The product yield increased with temperature and remained almost unchanged after 363 K (Fig. 1). In this case, conversion was ~100%.

The curve of the yield plotted against CO pressure passed through a maximum. As the pressure increased from 0.5 to 1.5 MPa, the yield increased from 65 to 98%. However, the yield decreased at pressures higher than 2 MPa, and it was equal to 75% at 5 MPa (Fig. 2).

In principle, the reaction can occur at atmospheric pressure; however, its rate is low. Butanol was used in place of methanol in order to increase the temperature of the reaction mixture (T_b = 391 K). However, even at 383 K, the yield of butyl acetoacetate was only 25% after 5 h. At 333 K, the absorption of CO occurred very slowly.

The concentration of a base also affected the rate of reaction. At the ratio Bu_3N/**1a** = 0.8, the yield of **2a** was only 42%. An increase in the concentration of Bu_3N resulted in an approximately linear increase in the yield up to 95% at Bu_3N/**1a** = 1.3. A further increase in the concentration of tributylamine to Bu_3N/**1a** = 1.5 caused an increase in the yield up to 98% (Fig. 3).

Thus, a temperature of 383 K, a pressure of 1.5 MPa, and a ratio of Bu_3N/**1a** = 1.5 are the optimum conditions. The carbonylation of other substrates **1** was performed under the optimum conditions found.

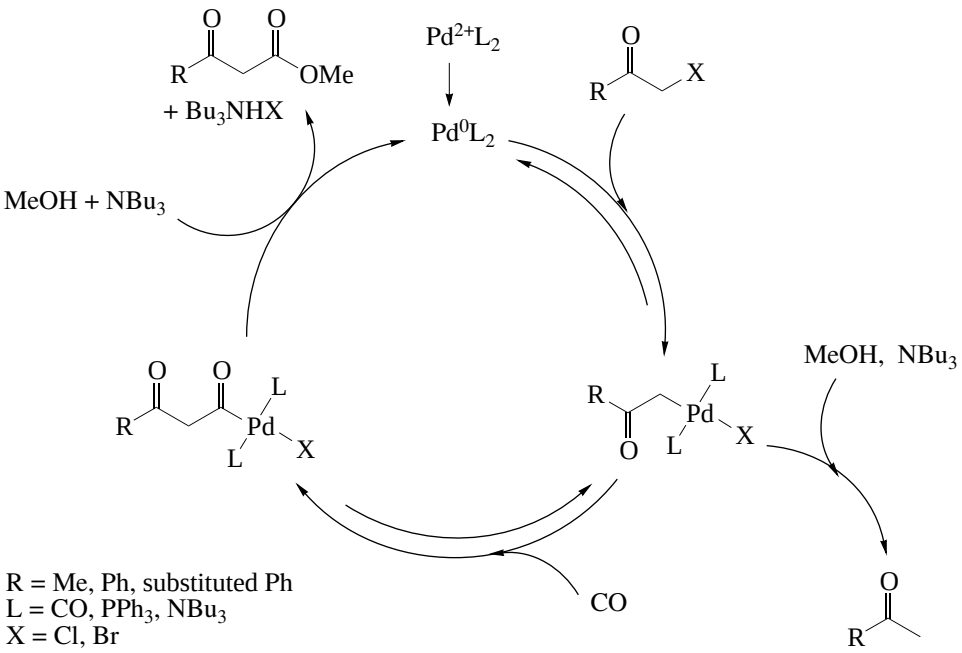
The experimental data suggest that the introduction of electron-acceptor substituents (F, Cl) into the aryl group of an aryl chloroalkyl ketone decreased the yield of the carbonylation product (see the table).

It is well known that bromo derivatives are carbonylated more readily than chloro derivatives. However, in this case, the reaction occurred more smoothly with α-chloroketones because the corresponding bromo derivatives were partially reduced to a ketone. Thus, α-bromoacetophenone formed only 53% carbonylation product and 33% acetophenone under optimum conditions (see the table).

We believe that the catalytic cycle of the carbonylation reaction of α-haloketones on Pd catalysts (scheme) includes the oxidative addition of a substrate to Pd(0) with the formation of an alkyl complex (which can undergo reduction as a side reaction), the migrational insertion of CO with the formation of an acyl complex, and the nucleophilic attack of methanol with the formation of product **2**. In this process, a base not only neutralizes the acid formed in the reaction but also catalyzes the alcoholysis of the acyl complex [25]. Taking into account the effect of the tributylamine concentration on the rate of reaction, we believe that the step of alcoholysis of the acyl complex under the given conditions is the rate-determining step.

It is well known that methoxycarbonyl complexes like $Pd(PPh_3)_2XCOOCH_3$ can be formed under the conditions of substitutive carbonylation reaction in the presence of tertiary amines [25, 26]. It was found that

Scheme proposed for the catalytic cycle



Scheme.

these complexes are inactive in carbonylation [25]. It is believed that the concentration of such a complex increased with increasing CO pressure; this is responsible for a decrease in conversion.

The reduction of an alkylpalladium intermediate (X = Br) leads to the formation of acetophenone as the main by-product of the synthesis. An analogous reduction of benzyl halides in toluene was observed in the case of two-phase carbonylation [27, 28]. This was explained by the homolytic cleavage of the Pd–C bond followed by hydrogen abstraction from the water molecule. In our case, in accordance with this mechanism, symmetrical 1,4-diketones should result from the combination of radicals. However, they were not detected in the reaction mixture. Moreover, it is unclear why substituted chloroketones **1a–1f** did not undergo reduction under the same conditions. In additional experiments, we found that bromoacetophenone can also be selectively reduced to acetophenone in the absence of CO (100% conversion and 73% yield). Moreover, either tributylamine or methanol can separately reduce bromoacetophenone in the presence of a palladium complex. In the latter case, formaldehyde was detected in the mixture.

In conclusion, note that the test carbonylation reaction of α-haloketones can serve as an additional general method for the synthesis of β-ketoesters.

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