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COBALT-CATALYZED SYNTHESIS OF α-ARYLPROPIONIC AND DIARYLACETIC ACIDS

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Summary

The cobalt-catalyzed carbonylation of ArCH(R)X (R = CH_3, C_6H_5; X = Cl, Br) in alcoholic solvents under atmospheric pressure of CO is reported. Selective, high yield syntheses of the corresponding acids ArCH(R)COOH can be achieved within a very narrow range of experimental conditions by controlling kinetically the reversible interconversion of intermediate aryl and alkylcobalt complexes. The important roles of the base and of the alcoholic medium are briefly discussed.

Introduction

We recently reported new cobalt-catalyzed carbonylation reactions of α-haloarylethanes under phase transfer conditions [1,2]. Secondary reactions such as hydrolysis, dehalogenation, dehydrohalogenation and coupling, and the presence among the reaction products of both branched and linear arylpropionic acids make the practical application of this reaction rather difficult. Nevertheless, selective formation of α-arylpropionic acids occurred in reasonable yields in the presence of suitable ammonium salts [1].

We suggested that secondary reactions could be curtailed if the reaction was appropriately kinetically controlled; this hypothesis has since been confirmed by an account of the mechanism of styrene hydroformylation [3], and this prompted us to attempt to overcome the synthetic limitations of the reaction.

Results and discussion

We report below the results of the cobalt-catalyzed, homogeneous phase carbonylation of secondary benzyl halides $ArCH(R)X$ (R = CH_3, C_6H_5) [4,5]. Either α-arylpropionic acids or diarylacetic acids, which are well-known important pharmaceutical products, were obtained in a selective, high-yield reaction under

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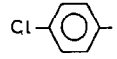
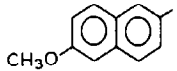
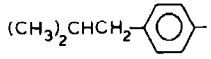
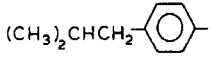
TABLE 1. CARBONYLATION OF α-HALOPHENYLETHANES $ArCH(CH_3)X$

Entry	Ar	X	Solvent	Base	T (°C)	Yield (%)		$ArCH(CH_3)X/Co$ ratio
						$ArCH(CH_3)COOH$	$ArCH_2CH_2COOH$	
1		Br	C_2H_5OH	NaOH	15	80	0	22
2 [a]		Br	C_2H_5OH	K_2CO_3	20	45	5	22
3		Br	C_2H_5OH/H_2O [b]	NaOH	20	62	6	22
4		Br	CH_3OH	NaOH	20	53	0	22
5		Br	CH_3OH	$Ca(OH)_2$	20	20	10	22
6		Cl	C_2H_5OH	NaOH	30	54	0	22
7		Br	C_2H_5OH	NaOH	15	70	0	22
8		Cl	i-C_3H_7OH	NaOH	15	58	0	9
9		Cl	i-C_3H_7OH	NaOH	35	70	0	30
10		Cl	C_2H_5OH	NaOH	20	75	0	40

[a] The products were recovered as ethyl esters. [b] $C_2H_5OH/H_2O = 5$.

surprisingly mild conditions (eq. 1):

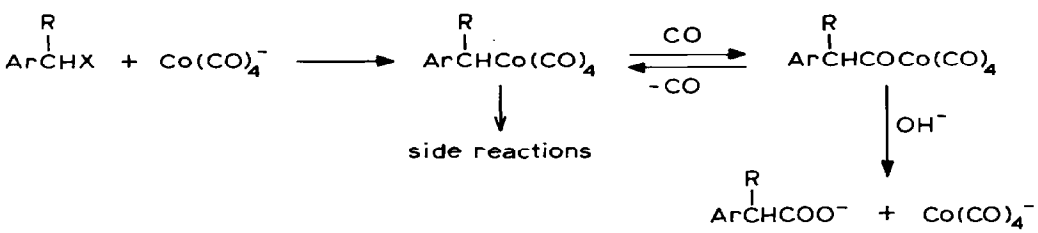
$$\mathrm{ArCHX} + \mathrm{CO} + 2\mathrm{OH}^- \xrightarrow[\mathrm{Co(CO)_4^-}]{\text{alcohol}} \mathrm{ArCHCOO}^- + \mathrm{X}^- + \mathrm{H_2O} \qquad (1)$$

(T 15–30°C; P(CO) 1 atm)

Alcohols were the most effective solvents, despite the fact that cobalt- or palladium-catalyzed carbonylation of α-haloarylethanes has been reported to be unselective in alcohol solution [6,7] and no carbonylation of halodiarylmethanes occurred in these media [6].

We chose alcohols as solvents because our previous studies had shown that they are among the best solvents for rapid formation of alkylcobalt complexes (see Scheme 1) [1,8]. Moreover, the good solubility of CO and bases in these media favours the rapid formation of acyl intermediates, and shifts the equilibrium between alkyl and acyl complexes towards the latter by irreversible formation of salts of carboxylic acids.

SCHEME 1

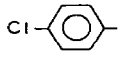
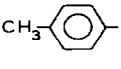


These favourable effects are fundamental in preventing the coupling of Co-bonded alkyl groups and the skeletal isomerization which are the main sources of side reactions. The combined effects of alcohols and bases operate simultaneously only within a very narrow range of experimental conditions, and, as shown in Tables 1 and 2, this explains previous failures. In Table 1 are listed the results obtained in the carbonylation of α-haloarylethanes. With α-bromophenylethane as a model substrate a yield of α-phenylpropionic acid as high as 80% was achieved with ethanol and NaOH. Under these conditions no β-isomer was formed (entry 1). By contrast, the highest yield reported in the literature for the α-isomer using NaOMe at controlled pH was 51%, and the β-isomer was still present to a significant extent (9% yield) [6].

In our case any change in the base (entries 2, 5) or solvent (entries 3, 4, 5) lowered the yield and/or selectivity. Side reactions account for the lower yield observed when starting from the less reactive α-chlorophenylethane (entry 6). It is noteworthy that α-(*p*-isobutylphenyl) propionic acid, a very important anti-inflammatory drug, was selectively obtained in good yield (75%) from the corresponding chloride with high catalytic efficiency ($\mathrm{ArCH(CH_3)X}$/Co ratio up to 40, entry 10). A 33% yield of the α-isomer and 2.5% yield of the β-isomer have been reported [6]. Racemic Naproxen (entry 8) was selectively obtained also; in this case the yield, based on the corresponding alcohol, was lower probably because of the high reactivity of the

TABLE 2

CARBONYLATION OF HALODIARYLMETHANES $ArCH(C_6H_5)X$

Nr.	Ar	X	Solvent	Base	T (°C)	Yield (%) of $ArCH(C_6H_5)COOH$	$ArCH(C_6H_5)X$/Co ratio
1		Cl	C_2H_5OH	NaOH	16	81.2	15
2		Cl	C_2H_5OH	NaOH	16	70	76
3		Cl	C_2H_5OH	K_2CO_3	25	–	15
4 [a]		Cl	CH_3OH	K_2CO_3	25	25	15
5		Cl	CH_3OH	NaOH	16	41.4	15
6		Cl	i-C_3H_7OH	NaOH	25	67	15
7		Br	C_2H_5OH	NaOH	10	46.7	15
8		Cl	C_2H_5OH	NaOH	16	62.8	15
9		Cl	C_2H_5OH	NaOH	16	68	15
10 [b]		Cl	n-C_4H_9OH/H_2O [c]	KOH (aq.) 50%	27	47.6	15

[a] The product was recovered as the methyl ester. [b] The reaction was carried out in the presence of phenyltrimethylammonium bromide (see Experimental). [c] n-$C_4H_9OH/H_2O = 1$.

starting chloride (formed in situ). The results obtained by carrying out the same reaction on halodiarylmethanes are shown in Table 2.

The carbonylation of halodiarylmethanes, although previously unknown, is not completely surprising, and we had in fact, noted indications that a facile interaction between $Co(CO)_4^-$ and halodiphenylmethanes could take place in hydrocarbon solvents [1]; we thus expected alcohols to promote carbonylation according to Scheme 1. The results obtained by carrying out the carbonylation of chlorodiphenylmethane in ethanol using NaOH as base (entries 1, 2) were very encouraging although unoptimized. The use of other alcohol-base pairs led to lower yields. Bromodiphenylmethane is a poorer starting material (entry 7) because alcoholysis is easier.

The reaction was also successfully performed with substrates bearing either electron-withdrawing or electron-releasing groups (entries 8, 9). The carbonylations described above are among the few examples of transition metal catalyzed reactions

not improved by the use of the phase transfer technique [9] (See entry 10 in Table 2 and ref. 10). The optimal conditions reached in a homogeneous phase can only be approached under phase transfer conditions by using suitable alcohols as the organic phase [1].

Conclusions

The results confirm the great importance of the choice of base and solvent for achieving a high-yield carbonylation of benzyl halides [11]. This means that not only the formation of the alkyl complex but also the nucleophilic attack of the base on the acyl complex are fundamental kinetic steps in the carbonylation of these compounds [12]. The reversible interconversion of the alkyl and the acyl complex may lead to many competitive reactions when substrates such as α-haloarylethanes are used. If this equilibration is allowed to proceed (leading to thermodynamic control) side reactions become significant, but when the equilibrium is rapidly shifted towards the acyl complex, by means of a fast irreversible nucleophilic attack by the base (kinetic control), selective, high-yield syntheses become possible.

Experimental

Materials. The secondary benzyl halides were commercially available or were prepared from the corresponding alcohols by standard procedures. α-Chloro-6-methoxy-2-naphthylethane was made as by a published method [13]. $NaCo(CO)_4$ was prepared by reduction of $Co_2(CO)_8$ with sodium amalgam in THF [14].

General procedure for preparation of acids under homogeneous conditions

Solvent (25 ml), alkali hydroxide (50 mmol), $NaCo(CO)_4$ (0.3–3 mmol) and the organic halide (25 mmol) were placed under CO in a flask (100 ml) equipped with magnetic stirrer and thermometer and connected to a burette filled with CO. The mixture was stirred at the relevant temperature until gas absorption stopped and was then acidified and worked up. The acids obtained were identified by IR, NMR and mass spectrometry of their derivatives. When two isomeric acids were present the composition of the mixture was determined by GLC analysis of their methyl esters.

Carbonylation of diphenylchloromethane under phase transfer conditions

n-Butyl alcohol (20 ml), KOH(aq.) 50% (20 ml), $NaCo(CO)_4$ (0.33 g, 1.7 mmol), diphenylchloromethane (25 mmol) and phenyltrimethylammonium bromide (0.5 g) were stirred together under CO at 27°C until CO absorption stopped (10 h). The mixture was then acidified and worked up to give 2.5 g of diphenylacetic acid (yield 47.6%).

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