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Regioselective synthesis of ibuprofen via the palladium complex catalyzed hydrocarboxylation of 1-(4-isobutylphenyl) ethanol

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Abstract

The synthesis of 2-(4-isobutylphenyl) propionic acid (ibuprofen) by the hydrocarboxylation of 1-(4-isobutylphenyl) ethanol with carbon monoxide and water has been studied in the presence of $PdCl_2$–PPh_3–HCl catalyst system. An almost regiospecific synthesis has been achieved under moderate reaction temperatures and pressures. In this reaction system, the liquid phases comprised of an acid-stable organic solvent and an acidic aqueous phase, and the miscibility between two phases were important for efficient hydrocarboxylation. The rate of reaction and the selectivity to the desired branched acid depended strongly upon the pressure of carbon monoxide, the ratio of phosphine ligand to palladium, the concentration of hydrochloric acid, and the nature of halide ion used.

Keywords: Synthesis of ibuprofen; Palladium complex; Hydrocarboxylation; Effects of halide ions; Regioselectivity

1. Introduction

There have been numerous patents and publications related to the hydrocarboxylation of alkenes and alcohols to carboxylic acids with carbon monoxide and water in the presence of palladium complex catalysts [1–12]. The reaction is the last step in a new process for the production of ibuprofen, a large-volume nonsteroidal anti-inflammatory drug. Among various processes developed for the manufacture of ibuprofen [13–19], the new process of Hoechst-Celanese involves three elegant catalytic steps, starting with 4-isobutylbenzene; catalytic acylation, hydrogenation, and carbonylation. For the carbonylation, they used $PdCl_2(PPh_3)_2$ catalyst and examined reaction variables such as solvent, hydrogen halide, CO pressure, and temperature [20]. More recently much attention has been paid to selective synthesis of the (*S*)-(+)-ibuprofen, the only enantiomer which has an active remedial effect [21–25].

Our previous studies [26,27] demonstrated that the highly regioselective carbonylation of 4-methylstyrene, the model compound of 4-isobutylstyrene, to 2-(4-methylphenyl) propionic acid, and its ester form could be achieved in the presence of $PdCl_2$-$CuCl_2$-PPh_3 catalysts. This paper relates to the preparation of 2-(4-isobutylphenyl) propionic acid, more commonly known as ibuprofen, from

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1-(4-isobutylphenyl) ethanol. Compared with our previous works on the hydrocarboxylation of 4-methylstyrene, the direct carbonylation of 1-(4-isobutylphenyl) ethanol would save a step of dehydration in a series of steps required to manufacture ibuprofen [28].

Usually drastic reaction conditions (exceedingly high pressure and strongly acidic medium) are required to effect the hydrocarboxylation of 1-(4-isobutylphenyl) ethanol in a selective way to 2-(4-isobutylphenyl) propionic acid (ibuprofen). We have applied $PdCl_2$–PPh_3–HCl catalyst system with several additives for the synthesis of ibuprofen under moderate conditions. Effects of various reaction conditions have been investigated, which include the nature of the palladium complex, the amount of phosphine ligand, the polarity of solvents, pressure, temperature, the concentration of hydrochloric acid, and the nature of halide ions. The optimum conditions were obtained by adjusting these variables of the reaction and catalysts system.

Since 1-(4-isobutylphenyl) ethanol was not commercially available, the substrate was prepared from 4-isobutylbenzene by two-step reactions. 4-Isobutylacetophenone was produced by Friedel–Crafts acylation of 4-isobutylbenzene, and then it was subjected to hydrogenation with 5 wt.% palladium on activated carbon to give 1-(4-isobutylphenyl) ethanol.

2. Experimental

The carbonylation was integrated with a method of producing 1-(4-isobutylphenyl) ethanol from 4-isobutylbenzene. The latter compound and a stoichiometric amount of aluminum chloride were mixed into CH_2Cl_2 solvent and cooled down to 233 K. Acetyl chloride was added, and the mixture was stirred for 2 h. When aqueous hydrochloric acid solution was removed, the acylation step was complete. For hydrogenation, a 300 ml stainless steel autoclave (Autoclave Engineers) was charged with 4-isobutylacetophenone, the product of the previous acylation reaction, together with ethanol solvent in the presence of palladium on activated carbon. It was pressurized to about 4 bar with H_2 and the contents were stirred at room temperature. The catalyst was filtered, and the solvent was evaporated to give 1-(4-isobutylphenyl) ethanol with more than 97% yield.

The hydrocarboxylation of 1-(4-isobutylphenyl) ethanol was performed in a 300 ml Hastelloy C autoclave reactor (Autoclave Engineers). Typically, 1-(4-isobutylphenyl) ethanol (5 g), palladium (II) chloride (0.04 g), triphenylphosphine (0.127 g) were dissolved in 3-pentanone (80 ml) and aqueous hydrochloric acid (0.014 M, 10 g) was added. The reactor was purged three times with CO (10 bar) and pressurized to 40 bar at room temperature, and the contents were heated to 398 K and kept at this temperature for the desired reaction time with vigorous stirring. During the reaction, the reaction mixture was sampled and analyzed by a gas chromatograph (GC, HP 5890 series II) with a 50 m DB-5 capillary column, and a flame ionization detector. The identification of GC peaks was done by using authentic samples and GC-Mass spectroscopy analysis (HP 5972 MSD). ^{1}H NMR, ^{13}C NMR, FT-IR spectra were recorded on a Bruker (AM 300 MHz) FT-NMR spectrometer, and a Bomem Michelson infrared spectrometer respectively.

3. Results

3.1. Characterization data of the substrate and products

Nearly pure 4-isobutylacetophenone (IBAP) was prepared by the Friedel–Craft acylation of 4-isobutylbenzene; MS $m/z = 176$, 161, 134, 119, 105, 91, 43; IR (KBr) $\nu = 3030$, 3003, 2926, 1684

(C=O), 1649, 1570, 1466, 1385, 1302, 1205, 1076, 1018, 851, 797, 692, 598; 1H NMR ($CDCl_3$) $\delta = 7.89$ (d, 2H), 7.22 (d, 2H), 2.57 (s, 3H), 2.52 (d, 2H), 1.88 (h, 1H), 0.91 (d, 6H); ^{13}C NMR ($CDCl_3$) $\delta = 198.2$ (1C=O), 148.0 (aromatic C), 135.3 (aromatic C), 129.7 (aromatic, 2CH), 128.8 (aromatic, 2CH), 45.8 ($1CH_2$), 30.6 (1CH), 27.0 ($1CH_3$), 22.8 ($2CH_3$). And then the hydrogenation of 4-isobutylacetophenone gave 1-(4-isobutylphenyl) ethanol (IBPE) in excellent yields of greater than 97%; MS $m/z = 178$, 163, 135, 121, 91, 57, 43; IR (KBr) $\nu = 3350$ (C–OH), 2955, 2868, 1678, 1514, 1466, 1383, 1283, 1202, 1119, 1020, 899, 847, 609, 555; ^1H NMR ($CDCl_3$) $\delta = 7.28$ (d, 2H), 7.14 (d, 2H), 4.84 (q, 1H OH), 2.49 (d, 2H), 1.89 (h, 1H), 1.48 (d, 3H), 0.95 (d, 6H); ^{13}C NMR ($CDCl_3$) $\delta = 144.6$ (aromatic C), 141.3 (aromatic C), 129.6 (aromatic, 2CH), 125.7 (aromatic, 2CH), 45.5 ($1CH_2$), 30.7 (1CH), 25.5 ($1CH_3$), 22.8 ($2CH_3$).

The main product obtained in hydrocarboxylation of IBPE was 2-(4-isobutylphenyl) propionic acid (IBPA (B)), i.e., ibuprofen; MS $m/z = 206$, 161, 119, 107, 65, 41; IR (KBr) $\nu = 3024$, 2995, 2926 (COOH), 1709 (C=O), 1512, 1426, 1412, 1285, 1188, 1123, 1022, 937, 847; ^1H NMR (pyridine) $\delta = 10.6$ (OH), 7.24 (d, 2H), 7.11 (d, 2H), 3.72 (q, 1H OH), 2.45 (d, 2H), 1.86 (h, 1H), 1.51 (d, 3H), 0.90 (d, 6H); ^{13}C NMR (pyridine) $\delta = 183.2$ (COOH), 142.8 (aromatic C), 141.6 (aromatic C), 131.3 (aromatic, 2CH), 129.8 (aromatic, 2CH), 46.9 ($1CH_2$), 32.1 (1CH), 24.3 ($1CH_3$), 20.0 ($2CH_3$). Other products include 3-(4-isobutylpheyl) propionic acid (IBPA (L)) which is the linear isomer of ibuprofen, 4-isobutylstyrene (IBS), 1-(4-isobutylpheyl) ethyl chloride (IBPCl), 4-isobutylpheylethane (IBE) and trace of a heavy component that was found to be a dimer of 4-isobutylstyrene. As described below, some of these by-products were detected only under certain reaction conditions.

3.2. The effect of IBPE / PD ratio

Table 1 shows the effect of mole ratio of IBPE to palladium complex catalyst while the ratio of the phosphine ligand to palladium was fixed at 2.2. When the IBPE/Pd mole ratio changed from 511 to 64 by increasing the amount of palladium for 5 g of IBPE, the conversion of IBPE increased only slightly because the conversion calculated from remaining IBPE was already 97.6% at IBPE/Pd ratio of 511. As the ratio decreased, the most conspicuous effect was the shift of selectivity from the dehydration product (IBS) to carbonylated products (IBPA). Furthermore, the selectivity to branched acid over linear isomer decreased. The turnover number (moles of IBPE converted per mole of palladium) could be improved by increasing the PPh_3 concentration as demonstrated in Run 5. Thus, even at high IBPE/Pd ratio of 1404, a high IBPE conversion and a good selectivity to ibuprofen were observed. The results also indicate that the role of the palladium complex is to catalyze the

Table 1
Hydrocarboxylation of IBPE with varied IBPE/Pd ratios[a]

IBPE/Pd (mol/mol)	Conversion of IBPE (%)	IBS	Selectivity (%)			B/L
			IBPCl	IBPA(B)	IBPA(L)	
511	97.6	27.4	5.1	66.5	0	∞[b]
255	99.6	0.4	0	98.9	0.6	138.2
128	100	0	0	98.0	2.0	47.8
64	100	0	0	93.3	6.7	14.0
1404[c]	99.5	5.6	0	92.8	1.6	58.3

[a] The following general procedure was used unless otherwise stated: IBPE = 5 g, PPh_3/Pd = 2.2, 10% HCl = 10 g, 3-pentanone = 81 ml, temperature = 398 K, CO pressure = 50 bar, reaction time = 13 h.
[b] Branched isomer only.
[c] IBPE = 25 g, PPh_3/Pd = 4.4, 3-pentanone = 120 ml.

carbonylation of the olefin intermediate (IBS) to the acid (IBPA). In the absence of the palladium catalyst, alcohol substrate was dehydrated to give IBS as the sole product. The reaction appeared to be catalyzed by the acidic medium.

3.3. The effect of solvent

The carbonylation of IBPE was very sensitive to the employed organic solvent as shown in Table 2. In toluene (Run 1), the conversion of IBPE was almost complete. But the reaction did not follow the usual pathway and gave unidentified by-products. Methyl-tertiary-butyl ether (Run 2) was unstable and gave undesired products that would be produced from a reaction between the solvent and reactants. In tetrahydrofuran, the dehydration product IBS was dominant with negligible formation of carbonylation products (Run 7), and many by-products were formed by the reaction between the solvent itself. Ketones were suitable for this carbonylation but cyclic ketone such as cyclohexanone (Run 6) could not tolerate the acidic condition and gave many by-products originating from the solvent. Although the methylethylketone was the popular solvent of industrial importance, about 10% of MEK was subjected to dimerization and isomerization probably because of the acidity of the present reaction medium. But the solvent did not react with substrate or other components in the reaction mixture, which was confirmed by a blank test with the solvent and aqueous hydrochloric acid only. 3-Pentanone showed good stability and selectivity to branched acid, and thus was our choice for the best reaction solvent. As shown in runs 8–10, the amount of employed solvent revealed a significant influence on the carbonylation rate. As the amount of MEK increased, the rate decreased as indicated by the increased amount of IBS, yet the ratio of B/L increased. Since the amount of the solvent would change the concentration of the involved species, it could be concluded that the reaction rate, as well as selectivity is dependent on the concentration of reactants and/or catalytic components in the reaction mixture.

3.4. The effect of solvent polarity

The effect of solvent polarity is summarized in Table 3. Adjusting the proportion of a nonpolar solvent (cyclohexane) relative to 3-pentanone would change the polarity. As the polarity decreased by

Table 2
The effect of solvents on the hydrocarboxylation of IBPE[a]

Run	Solvent	Volume (ml)	Conversion of IBPE (%)	Selectivity			B/L
				IBS	IBPA(B)	IBPA(L)	
1	Toluene	27	98.7	19.5	11.2	0	∞
2	MTBE	27	84.8	26.3	0	0	–
3	Acetone	27	98.1	1.7	76.1	22.1	3.4
4[b]	MEK	81	100	0	97.0	3.0	32.7
5[b]	3-Pentanone	81	100	0	97.4	2.6	36.9
6[b]	Cyclohexanone	81	78.7	0	14.8	0	∞
7[b]	THF	81	91.3	89.7	6.3	3.9	1.6
8[c]	MEK	27	100	2.6	87.3	10.1	8.7
9[c]	MEK	54	100	16.1	79.8	4.1	19.4
10[c]	MEK	81	100	18.1	80.2	1.7	46.8

[a] IBPE = 5 g, PPh_3/Pd = 4.4, 10% HCl = 25 g, H_2SO_4 = 1 ml, temperature = 398 K, CO pressure = 50 bar, reaction time = 13 h.
[b] PPh_3/Pd = 2.2, without H_2SO_4, otherwise the same conditions as in a.
[c] PPh_3/Pd = 2.2, otherwise the same conditions as in a.

Table 3
The effect of solvent's polarity on the hydrocarboxylation of IBPE[a]

Run	3-Pentanone (ml)	Cyclohexane (ml)	Conversion of IBPE (%)	Selectivity (%)				B/L
				IBS	IBPA(B)	IBPA(L)	dimer	
1[b]	81	0	98.4	3.0	93.5	3.1	0.4	30.2
2[b]	81	10	90.4	8.1	91.9	0	0	∞
3[b]	60	20	70.3	27.1	64.7	0	8.3	∞
4[b]	40	40	46.7	34.1	50.0	0	17.9	∞
5[c]	81	0	100	0	84.1	15.9	0	5.3
6[c,d]	81	10	98.1	1.9	79.4	15.5	3.0	5.1
7[c]	40	40	55.2	34.0	35.6	8.8	21.5	4.0
8	Benzene	81 ml	31.0	51.9	7.07	0	41.1	∞

[a] IBPE = 5 g, PPh_3/Pd = 2.2, 10% HCl = 5 g, temperature = 398 K, CO pressure = 40 bar, reaction time = 13 h.
[b] 5% HCl = 10 g.
[c] 5% HBr = 10 g.
[d] Reaction time = 7 h.

adding increased amounts of cyclohexane (Run 1–4, Run 8), the carbonylation rate was slowed down as indicated by reduced IBPE conversions and increased formation of IBS. A slight increase in selectivity to branch acid was also observed. It was found that the nonpolar solvent made a clear phase separation between aqueous and organic phases. The formation of undesirable heavy compounds could be prevented by adding a polymerization inhibitor such as *t*-butylcatechol, hydroquinone, or *m*-dinitrobenzene [20]. When HBr was used instead of HCl (Run 5–7), the reduced polarity of solvent had no favorable effect on the mole ratio of branched acid over linear acid (B/L) although the reaction rate decreased exceedingly. Thus, it appears that the selectivity to branch acid over linear isomer is affected by the nature of halide ions as well. As the reaction occurred in the organic phase, the difference in solubility of water according to the polarity of organic solvent could be a very important factor for the reaction rate. It has been reported that the solubility of carbon monoxide does not play an important role in the reaction rate as the polarity of solvent is changed [29].

3.5. The effect of triphenylphosphine

Palladium catalysts used in the carbonylation of IBPE require an appropriate phosphine ligand, in the present case, triphenylphosphine (PPh_3). The palladium (II) chloride and triphenylphosphine were added separately to the reaction mixture and the catalytic complex, bis(triphenylphosphine) palladium dichloride, $PdCl_2(PPh_3)_2$, which is formed in situ is known to be stable and an active catalyst for the carbonylation of olefins [20]. In fact, we observed orange crystalline precipitates after the reaction, which were believed to be $PdCl_2(PPh_3)_2$ [30]. In some cases, a mirror of palladium metal was formed on the wall of the reaction vessel. Tsuji et al. reported that $PdCl_2$ in aqueous or alcohol solution was readily reduced to the metal by carbon monoxide [31]. The effects of PPh_3 are summarized in Table 4. Without PPh_3 added (Run 4), only the dehydration reaction occurred, which revealed that, together with $PdCl_2$, PPh_3 was the essential component of the catalyst complex for the carbonylation step. Although there were slight differences in reaction conditions between runs reported in Table 4 as noted, the general trend was that the increase of PPh_3/Pd mole ratio improved the reaction rate but reduced the selectivity to the branch acid. There have been many reports in which excess phosphine was used in order to prevent the decomposition of palladium–phosphine ligand complexes [10].

Table 4
The effect of triphenylphosphine (PPh_3) on the hydrocarboxylation of IBPE[a]

Run	PPh_3/Pd	Conversion of IBPE (%)	Selectivity (%)				B/L
			IBS	IBPCl	IBPA(B)	IBPA(L)	
1	2.2	92.7	54.5	0	39.9	5.7	7.0
2	4.4	93.9	45.1	0	43.6	11.2	3.9
3	44	100	7.0	0	37.7	55.3	0.68
4[b]	0	97.1	94.2	5.8	0	0	–
5[b]	2.2	100	0	0	98.0	2.0	49.0
6[b]	4.4	100	0	0	95.4	4.6	20.7
7[c]	4	99.1	0.8	0	97.5	6.0	14.6

[a] IBPE = 5 g, $PdCl_2$ = 0.039 g, 3.2% HCl = 25 g, $CuCl_2$ = 0.17 g, H_2SO_4 = 1 ml, MEK = 27 ml, temperature = 398 K, CO pressure = 50 bar, reaction time = 13 h.
[b] 10% HCl = 10 g, 3-pentanone = 81 ml.
[c] $Pd(PPh_3)_4$ = 0.231 g, 5% HCl = 10 g, CO pressure = 40 bar, without H_2SO_4.

However, excessive amounts of phosphine ligand (Run 3) could invert the B/L mole ratio. Therefore, a phosphine to palladium ratio of about two was found to be the optimum for the rate and selectivity of the carbonylation reaction. Of course, this is the ratio of PPh_3/Pd in $PdCl_2$ $(PPh_3)_2$ that is the suspected active catalytic species. When the mole ratio of PPh_3/Pd was far greater than 4, more reduced palladium complexes such as $Pd(0)(PPh_3)_4$ could be formed and affect the selectivity to the branch acid. In Run 7, the pre-synthesized $Pd(PPh_3)_4$ was used instead of $PdCl_2$ and PPh_3. The selectivity was not very different from that observed for $PPh_3/PdCl_2$ ratios of 2.2 or 4.4, although the reaction rate at the early stage was little bit slower. Probably, with sufficient amount of HCl around, $Pd(PPh_3)_4$ would have converted to the effective $PdCl_2(PPh_3)_2$ complex during the reaction.

3.6. The effect of CO pressure and reaction temperature

The pressure of carbon monoxide had a profound effect on the carbonylation reaction as shown in Fig. 1, where changes with time of each component in the reaction mixture are compared for 40 bar and 10 bar of CO pressure. The general shape of these time–concentration curves indicates that IBS is the main reaction intermediate, and that the branch and linear forms of IBPA are formed in parallel

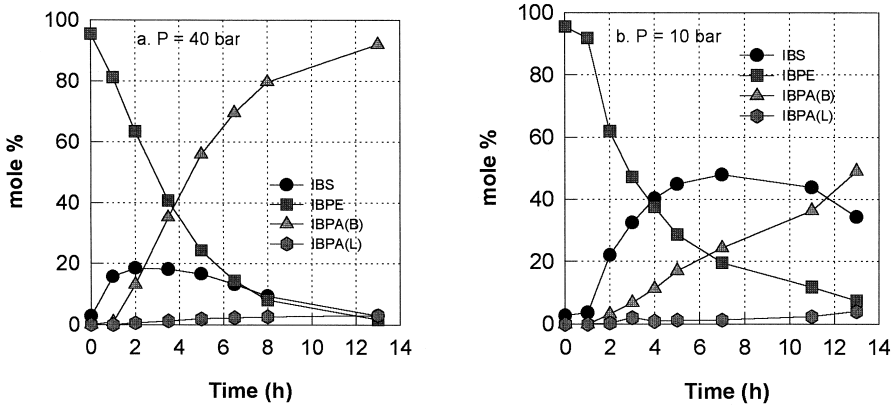


Fig. 1. Effects of CO pressure on the hydrocarboxylation of IBPE: (a) 40 bar (b) 10 bar; IBPE = 5 g, Pd/PPh_3 = 2.2, 10% HCl = 10 g, 3-pentanone = 81 ml, temperature = 398 K, reaction time = 13 h.

Table 5
The effect of carbon monoxide pressure on hydrocarboxylation of IBPE[a]

Run	CO (bar)	N_2 (bar)	Conversion of IBPE (%)	Selectivity (%)				B/L
				IBS	IBPCl	IBPA(B)	IBPA(L)	
1	10	–	100	0	0	85.4	14.6	5.8
2	20	–	100	0	0	93.3	6.7	13.9
3	30	–	100	0	0	95.5	4.5	21.2
4	40	–	100	0	0	97.6	2.4	40.7
5	50	–	100	0	0	98.0	2.0	49
6[b]	10	30	94.3	25.5	2.9	62.0	9.7	6.4

[a] IBPE = 5 g, Pd/PPh_3 = 2.2, 10% HCl = 10 g, 3-pentanone = 81 ml, temperature = 398 K, reaction time = 13 h.
[b] 5% HCl = 10 g.

steps. The rate of IBPE conversion was almost independent of CO pressure, but the formation of ibuprofen was much faster at the higher pressure. This indicates that the concentration of carbon monoxide is important for the carbonylation step of IBS. At 10 bar, IBS was the major product during the most of the reaction time whereas at 40 bar, it was a dominant product only in the early stage of the reaction. The effect of CO pressure was studied for 10 bar to 50 bar and the results after 13 h of reaction time are summarized in Table 5. The rate of carbonylation reaction increased apparently as the pressure increased. But complete conversion was achieved for all pressures after 13 h. In the carbonylation of 1-octene to synthesize a linear saturated acid, Alper [11] noted that an increase in the carbon monoxide pressure caused an increase in the yield of acid products nearly in first order. A more significant effect was observed for the B/L ratio. Higher CO pressures gave higher B/L ratios. When the total reaction pressure was maintained at 40 bar with 10 bar of CO balanced with nitrogen gas (Run 6), the results were similar to those for 10 bar of pure CO, indicating that partial pressure of CO is important. This implies that abundant CO that dissolved in the liquid phase is very important for the carbonylation rate and selectivity [12,26].

Effects of reaction temperature are shown in Fig. 2 for 373 K and 423 K. At 373 K, the conversion of IBPE was only 34%, the selectivity to the branch acid was 18%, and the linear isomer was not produced. The overall reaction proceeded more rapidly, and the B/L ratio decreased from infinity to about 20 as the reaction temperature increased from 373 to 423 K. When the reaction was carried out at 373 K, the reaction was slow due to both the slow dehydration step and slow carbonylation step. In

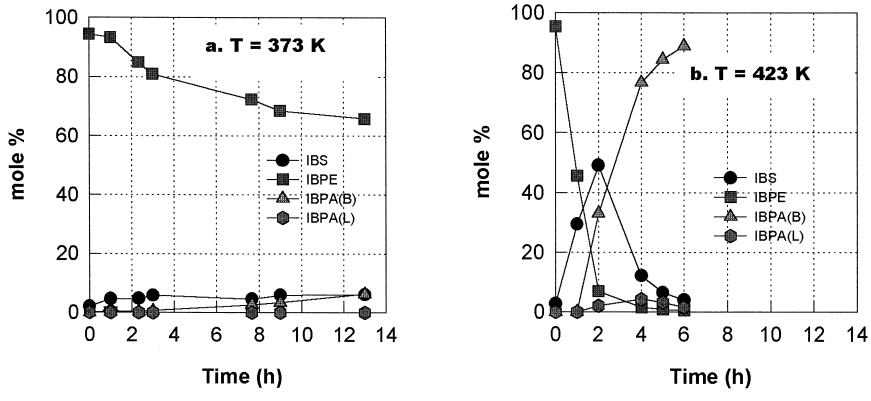


Fig. 2. Effects of reaction temperature on the hydrocarboxylation of IBPE: (a) 373 K, (b) 423 K; IBPE = 5 g, Pd/PPh3 = 2.2, 10% HCl = 5 g, 3-pentanone = 81 ml, H_2O = 5 g, CO pressure = 40 bar, reaction time = 13 h.

Table 6
The hydrocarboxylation of IBPE with ion-exchange resin[a]

Run	Conversion of IBPE (%)	Selectivity (%)				B/L
		IBS	IBPCl	IBPA (B)	IBPA (L)	
1[b]	34.2	18.0	30.18	18.4	0	∞
2	96.3	49.0	0	51.0	0	∞
3[c]	97.5	36.1	2.4	61.5	0	∞

[a]The following general procedure was used unless otherwise stated: IBPE = 5 g, Pd/PPh_3 = 2.2, 5% HCl = 10 g, 3-pentanone = 81 ml, temperature = 398 K, CO pressure = 40 bar, reaction time = 13 h.
[b]Temperature = 373 K, without HCl. The remaining balance for 100% in selectivity was a dimer of IBS. Amberlyst® 15-ion exchange resin = 5 g.
[c]Tetrabutylammonium chloride = 0.3807 g.

an attempt to improve the slow rate of dehydration at 373 K as indicated by the small conversion of IBPE, Amberlyst 15 was employed as an additional dehydrating catalyst (Table 6, Run 2). Amberlyst 15 is a strongly acidic cation exchange resin with built in macropores manufactured by Rohm and Hass. In contrast to the reaction in the absence of the ion exchange resin (Run 1), the concentration of carbonylated products increased, which indicated that the dehydration was the rate-determining step in the carbonylation of IBPE. Even in the absence of the hydrogen halide with only the resin as an acid catalyst the carbonylation took place to produce the branched IBPA. Additional chloride ion supplied as tetrabutylammonium chloride helped the carbonylation occur faster giving a higher yield of IBPA (Run 3).

3.7. The effect of hydrochloric acid

Table 7 shows the effect of hydrochloric acid concentration in the aqueous phase and total amount of added aqueous phase. The amount of aqueous phase containing HCl was the important factor for the selective hydrocarboxylation. The carbonylation of IBPE hardly occurred in the absence of HCl (Run 1). If the aqueous phase was less than 5% of liquid phase by mass the yield of ibuprofen decreased even though the substrate was completely consumed (Run 2). It appears that the lack of water in the organic phase lead to dimerization of IBS. Too great a quantity of aqueous phase, however, lowered the B/L ratio of ibuprofen (Run 5). In Runs 4, 6, 7, the mass of aqueous phase was

Table 7
The effect of the hydrochloric acid on the hydrocarboxylation of IBPE[a]

Run	Aqueous Phase (g)	HCl(M)	Conversion of IBPE (%)	Selectivity (%)				B/L
				IBS	IBPA (B)	IBPA (L)	Dimer	
1	10	0	23.8	72.0	0	0	28.0	
2	2.5	2.74	98.9	0.7	19.8	0	78.6	∞
3	5	2.74	100	0	71.8	1.6	22.6	44.9
4	10	2.74	100	0	98.0	2.0	0	49
5	25	2.74	100	0	97.4	2.6	0	36.9
6	10	1.37	100	0.8	95.8	3.4	0	28.5
7	10	0.68	78.8	37.3	57.0	1.8	0	31.7
8	40	0.34	34.9	68.2	5.7	0	9.2	∞

[a]IBPE = 5 g, Pd/PPh_3 = 2.2, 3-pentanone = 81 ml, temperature = 398 K, CO pressure = 40 bar, reaction time = 13 h.

fixed, and the concentration of hydrochloric acid was varied. As the concentration of HCl became higher, the carbonylation proceeded more rapidly without any considerable change in B/L ratio. When the concentration was too low, both conversion of IBPE and selectivity to IBPA were low, indicating slow rates of both dehydration and carbonylation steps. When the fraction of aqueous phase was over 30–50% of liquid phase (Run 8), the phase separation seems to be serious enough to limit mass transfer of water, which was also one of the reactants [11]. The other possibility is that the reduced effective concentration of HCl that would distribute itself preferentially into aqueous phase. In order to discern these two possibilities, the amount of aqueous phase and HCl were increased simultaneously. Then, the drop of the carbonylation rate was disappeared. Hence, it was concluded that the slow rate of reaction at high water loading was not due to the low concentration of water, but due to the low concentration of HCl in the organic phase. Irrespective of the phase separation, it appears that the organic phase is saturated with water at the high water loading.

To the best of our knowledge, there have been few reports concerning the effect of halide ion on the carbonylation of IBPE. The effect of the nature of hydrogen halide is shown in Table 8. When Br or I was employed, the reaction rate increased slightly whereas the B/L ratio decreased slightly relative to the case with Cl. In the case of HF (Run 5), the reaction was extremely slow and the carbonylation step did not occur at all. Interestingly, when HI was added in place of generally used HCl or HBr, the hydrogenation of IBPE or IBS occurred and gave the fully hydrogenated product, (4-isobutylphenyl)ethane (IBE). The presence of water would make it possible to form hydrogen via the water–gas shift reaction.

$$CO + H_2O \rightleftarrows CO_2 + H_2 \quad (1)$$

The hydrogen could lead to the formation of IBE by hydrogenation of the olefin, IBS.

In order to separate effects of proton and chloride ion, sulfuric acid and metal halides were used as proton and chloride ion sources respectively (Table 9). When only sulfuric acid was employed, IBS was formed predominantly (Run 2). Even though there was no halide ion added, a small amount of IBPA was produced probably because the chloride ion was available from the palladium(II) chloride catalyst precursor. It appears that H_2SO_4 promotes the dehydration effectively, yet is totally ineffective in carbonylation. When only KCl was provided (Run 3), the reaction did not take place for 13 h. In the absence of a proton source, the initial dehydration step does not proceed and, as a result, the subsequent carbonylation step does not take place either. In Run 4, proton and chloride ions were supplied together, then, ibuprofen was synthesized in a good yield. This suggests that the conversion of IBPE to ibuprofen requires the presence of a proton, as well as halide ion. NaCl was used instead of KCl in Run 5, and, the result was similar. When sulfuric acid was present with HCl (Run 6), more

Table 8
The effect of halide ions on the hydrocarboxylation of IBPE[a]

Run	10% HX (g)	H_2O (g) (g)	X (mmol)	Conversion of IBPE	Selectivity (%)					B/L
					IBE	IBS	IBPA (B)	IBPA (L)	Dimer	
1	HCl 5	5	14	98.4	0	3.0	93.5	3.1	0.4	30.2
2	HBr 5	5	6.2	100	0	0	84.1	15.9	0	5.3
3	HBr 1	9	1.2	69.7	0	47.0	39.6	8.4	5.0	4.7
4[b]	HI 5	5	4.0	100	39.9	0	38.4	22.3	0	1.7
5	HF 5	5	25	35.3	0	63.0	0	0	39.8	–

[a] IBPE = 5 g, Pd/PPh_3 = 2.2, 3-pentanone = 81 ml, temperature = 398 K, CO pressure = 40 bar, reaction time = 13 h.
[b] Reaction time = 5 h.

Table 9
The effect of hydrogen ion and chloride ion on the hydrocarboxylation of IBPE[a]

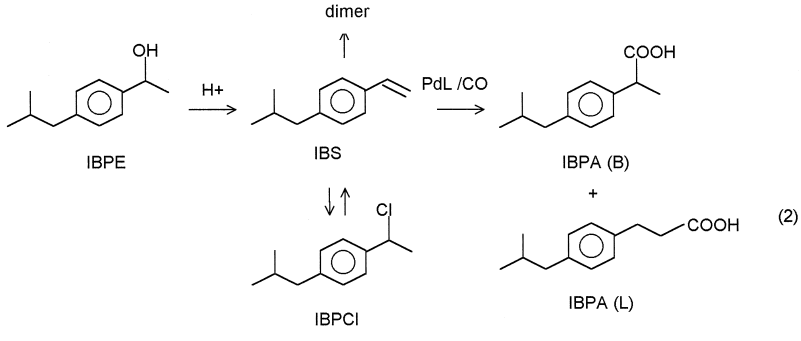
Run	H_2SO_4 (mmol)	Cl (mmol)	Conversion of IBPE (%)	Selectivity (%)			B/L
				IBS	IBPA(B)	IBPA(L)	
1	0	HCl 27	98.4	3.0	93.5	3.1	30.2
2	27	0	94.1	92.5	7.0	0.5	14.0
3	0	KCl 27	0	0	0	0	–
4	27	KCl 27	100	23.4	76.6	0	∞
5[b]	27	NaCl 27	96.0	15.5	70.0	0.8	87.5
6[b]	14	HCl	93.4	33.7	64.2	1.7	37.7
7[c]	14	HCl 27	94.8	36.3	60.4	0	∞
8[d]	0	$SnCl_2$ 0.2 HCl 27	89.4	88.3	1.2	0.2	6.0

[a] IBPE = 5 g, Pd/PPh_3 = 2.2, 3-pentanone = 81 ml, Temperature = 398 K, CO pressure = 50 bar, reaction time = 13 h.
[b] 5% HCl = 10 g, CO pressure = 40 bar.
[c] Palladium sulfate = 0.0405 g, 5% HCl = 10 g, CO pressure = 40 bar. The remaining balance for 100% is for IBPCl.
[d] $SnCl_2 \cdot 2H_2O$ = 0.0452 g, 5% HCl = 10 g, CO pressure = 40 bar. The remaining balance for 100% is for IBPCl (5.3%) and IBE (5.0%).

IBS was formed, yet the carbonylation rate decreased compared to the resin obtained in Run 1 with only HCl. Sulfate ion could partly poison the palladium catalyst which was confirmed by using palladium(II) sulfate precursor instead of palladium chloride (Run 7). The result was similar to the one in Run 6 with $PdCl_2$, HCl and H_2SO_4. Tin chloride was introduced in Run 8 because it has been reported to assist the formation of a hydride for the palladium complex [32]. Yet the addition of $SnCl_2$ retarded the rate of reaction and lowered the ratio of branch to linear acid.

4. Discussion

The hydrocarboxylation of IBPE to ibuprofen was achieved with an excellent regiospecificity in the presence of $PdCl_2$–PPh_3–HCl. Important reaction variables that affect the reaction rate and selectivity to branched IBPA were the amount of catalytic complex, solvent, the ratio of phosphine ligand to palladium, pressure, temperature, and the nature of halide ion used. The concentration–time behavior and effects of these reaction variables are consistent with the reaction sequence as depicted in Eq. (2).



(2)

A strong protonic acid solely catalyzes the dehydration of IBPE. Mineral acids such as HCl, H_2SO_4 and the acidic cation exchange resin were found to be equally effective catalysts. When HCl or other chlorine-containing agents are employed, the formation of IBPCl is observed, if the subsequent carbonylation step is not efficient.

The reaction rate and selectivity to the desired ibuprofen or IBPA(B) depend on the reactivity of the major intermediate IBS. Under the conditions when the carbonylation step is not fast enough, its concentration builds up and it partly transforms to the dimer. The concentration of IBPCl follows the same trend as that of IBS, indicating that it is also an important intermediate when chlorine is present in the system.

The rate of carbonylation and its selectivity depend on many variables in a complicated way. First, the reaction conditions should be adjusted to favor the formation of $PdCl_2(PPh_3)_2$, which appears to be the active catalytic species. In the present system, the species is formed in situ when we employ a catalytic system of $PdCl_2$–PPh_3–HCl. As described, both PPh_3 and HCl are essential components for the Pd catalyst to perform the carbonylation effectively. If amount of these promoters is insufficient, the rate of carbonylation is too slow. Under the highly reducing conditions of the present reaction systems, caused by the presence of CO and water, Pd(0) species or Pd particles are easily formed which are inactive for the carbonylation. It is well known that chlorine stabilizes a divalent Pd complex [33] and that PPh_3 stabilizes a molecular Pd species and prevents the formation of bulk Pd particle [34]. However, an excessive amount of promoters reduce the B/L ratio as shown in Table 4 and in our previous study of hydrocarboxylation of 4-methylstyrene [27].

It is important to note here the dual role of HCl; to provide the proton that promotes the dehydration of IBPE and to provide chlorine that promotes the carbonylation step. As mentioned, there has been no discussion in the literature on the role of halide ions, although HCl has been reported as an essential promoter in hydrocarboxylation [27]. Schoenberg et al. [35] proposed that electron withdrawing substituents on the aryl ring increase the rate of carbonylation of aryl halides. However, the effect appears to be irrelevant to the present case because there is no indication that halide ions added to the reaction system would react with the aromatic ring of the substituents. As shown previously in the hydrocarboxylation of 4-methylstyrene [27], halide ions are believed to act as ligands of the active Pd catalyst complex, and stabilize Pd (II). Apparently, chlorine is most effective for this role.

The second important condition for effective carbonylation of IBS is an intimate contact between organic reactants and water. As water is one of the reactants, its high solubility in organic reactants and catalyst is required. The choice of solvent and amount of water added to the reaction system are dictated by this requirement. As a solvent, 3-pentanone was found to be effective and stable during the reaction under the strongly acidic conditions. It has a moderate polarity to dissolve enough water to react with the organic phase. As a reactant, a certain amount of water would be required to obtain high reaction rates. However, an excessive amount of water seems to cause separation of aqueous and organic phases and reduce the effective concentration of water in the organic phase.

In most cases, the branched isomer of IBPA is the main product of carbonylation. However, its concentration relative to the linear isomer (B/L ratio) shows a complicated dependence on many reaction variables. In general, two isomers appear to be produced in parallel steps because there is no consistent dependence of the B/L ratio on the conversion of the reactant. The strong effect of CO pressure and amount of PPh_3 on the B/L ratio is interesting, but its origin is not clear. The halide ion is one of the main factors determining the rate of carbonylation and the selectivity to branch acid.

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