Synthesis of aromatic acids via catalyzed methyl formate–chloroarene reactions ‡

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Abstract

Chlorobenzene and more generally, chloroarenes, can be converted into aromatic acids via catalytic reaction with aqueous methyl formate under biphasic conditions. The only efficient catalyst is $[PdCl_2(PCy_3)_2]$ (Cy = cyclohexyl). $[Ru_3(CO)_{12}]$ and ammonium formate improve yield and selectivity. The mechanism should involve oxidative addition of the C–Cl bond to a zero-valent Pd species followed by CO insertion. The palladium catalyst may also directly activate methyl formate. The procedure is convenient (no solvent, no initial pressurization) and at least as efficient as previously described methods.

Key words: Palladium; Ruthenium; Catalysis; Carbonylation; Chloroarene

1. Introduction

Carbonylation of carbon-halide bonds in aromatic halides is of wide industrial application field. It is a promising method for the synthesis of commercial aromatic acids, useful intermediates for the manufacture of plasticizers, dyes, food preservatives, flavours, pharmaceuticals, and other chemicals (benzoates, benzoyl chloride). Unlike C–Br and C–I bonds, carbon–chlorine bonds have proved to be exceptionally resistant to catalytic cleavage [1*] †. Activation of the C–Cl bond in chloroarenes has been achieved in the last few years essentially *via* palladium-catalyzed carbonylation, either homogeneously under chelate assistance [2], or heterogeneously [3]. Alkoxycarbonylation of chloroarenes complexed to $Cr(CO)_3$ in the presence of $[PdCl_2L_2]$ (L = phosphine) [4,5] is easier, but with reduced selectivity [5]. Two recent articles report the carbonylation of simple chloroarenes catalyzed by dichloro-bis(tricyclohexylphosphine)palladium [6,7]. The phosphine unquestionably exerts strong directive effect.

For some years, our laboratory has been using methyl formate as a CO alternative. This ester undergoes selective decarbonylation at 180°C under ruthenium catalysis in the presence of PCy_3 [8]. The property was previously evident in the alkoxycarbonylation of ethylene [9]. In addition, methyl-formate-mediated carbonylation of ethylene to ketones was recently achieved [10]. These results, together with those reported in refs. 6,7, suggested the possible synthesis of benzoic acid *via* methyl-formate-mediated carbonylation of chlorobenzene (in the absence of initial carbon monoxide). In addition, formates were already used in the carbonylation of benzyl and alkyl chlorides catalyzed by a dimeric rhodium complex [11]. However, that reaction requires initial carbon monoxide, does not occur with methyl formate, and is not applicable to aryl chlorides.

2. Experimental details

The palladium catalyst $[PdCl_2L_2]$ was prepared as described elsewhere (yield 80%) [12]. In a typical run, chlorobenzene (1 cm^3, 9.85 mmol), methyl formate (3

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† Reference number with asterisk indicates a note in the list of references.

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cm^3, 48.6 mmol), water (1 cm^3), potassium hydroxide (500 mg, 8.9 mmol), Pd catalyst (0.024 mmol), $[Ru_3(CO)_{12}]$ (0.007 mmol), cetyltrimethylammonium bromide (100 mg, 0.27 mmol), mesitylene (200 μl, chromatographic standard) were placed in a 15-ml stainless steel autoclave which was closed, heated to 160°C and shaken for 10 h.

After cooling, the vessel was vented. The liquid mixture was collected and water (5 cm^3) was added. The organic layer was dried and analyzed by GC: Girdel 300 (FID), PPE 7% on Chromosorb G AW. DMCS (Pyrex), 60–230°C, 5°C min^{-1}. The aqueous layer was neutralized by HCl. The carboxylic acids were extracted with 4×7 cm^3 ether, weighed and analyzed by IR spectroscopy and their spectra were compared to those of authentic compounds. In some cases, NMR spectroscopy was also used. The products isolated from the runs carried out with chlorophenols were heated under reflux in methanol in the presence of some drops of sulfuric acid. The mixtures were submitted to GC analysis and the products identified as the corresponding methyl esters.

3. Results and discussion

We carried out the carbonylation runs under biphasic conditions (aqueous KOH) with methyl formate as the carbonylation agent (see Experimental section). Ruthenium catalysis is inefficient for the synthesis of aromatic acids, despite complete decomposition of the formate ester under the conditions described in Table 1.

Simple palladium catalysts ($Pd/BaSO_4$ and $PdCl_2$) were also inactive. The complex catalyst $[PdCl_2(PCy_3)_2]$ (abbreviated PCPC) led to benzoic acid in 9% yield, consistent with previous results [6,7]. Addition of a small amount of $[Ru_3(CO)_{12}]$ (8×10^{-3} mmol) (the required concentration may be less) improved this yield (12.7%). In contrast with ref. 6, the Pd catalyst did not form *in situ* (*cf.* entries 3 and 5) meaning that initial reducing conditions (presence of CO) are required to generate the active catalyst. Accordingly, all further experiments were carried out with the binary catalytic system PCPC + $[Ru_3(CO)_{12}]$. The products were benzoic acid and benzene.

The reaction products depend on temperature. Best yields of benzoic acid were obtained at 160°C. Lower temperatures produced reduced yields, presumably due to a decrease in the decarbonylation rate of methyl formate and therefore less CO. Higher temperatures were beneficial for decomposition of the formate ester but favoured decarboxylation rather than decarbonylation; at 180°C, composition of the gas mixture after 5 h (without initial addition of chlorobenzene) was CO (20%), CO_2 (61%), H_2 (9%), CH_4 (10%) whereas at 160°C, analysis gave CO (56%), CO_2 (31%), H_2 (11%) CH_4 (2%). The yield of benzoic acid was therefore dependent on the concentration or partial pressure of CO. This was also highlighted in the run using 5 cm^3 methyl formate (entry 6) instead of 3 cm^3 (entry 5); the yield was increased by 50%.

TABLE 1. Carbonylation of chlorobenzene by methyl formate [a]

Entry	Catalyst	Additives [b]	T (°C)	Yields [c] (%)	
				ArCOOH	ArH
1	$Pd/BaSO_4$	CTAB	160	0	nd
2	$PdCl_2$	CTAB	160	0	nd
3 [d]	$PdCl_2$, Ru	PCy_3 [d], CTAB	160	0.8	6.5
4	PCPC	CTAB	160	9.0	8.1
5	PCPC, Ru	CTAB	160	12.7	3.5
6 [e]	PCPC, Ru	CTAB	160	18.2	nd
7 [f]	PCPC, Ru	CTAB	160	5.0	nd
8 [f]	PCPC, Ru	None	160	0.6	nd
9	PCPC, Ru	CTAB	140	5.2	nd
10	PCPC, Ru	CTAB	180	10.8	3.7
11	PCPC, Ru	None	180	7.2	2.1
12 [e]	PCPC, Ru	PCy_3 [g], CTAB	160	15.8	3.7
13 [e]	PCPC, Ru	AF [h], CTAB	160	35.8	0
14 [e]	PCPC, Ru	AF [h], CTAB	160	19.2	0
15 [e]	PCPC, Ru	AF [i], CTAB	160	2.2	4.2

[a] Conditions as described in the experimental part. PCPC was $[PdCl_2(PCy_3)_2]$ and Ru was $[Ru_3(CO)_{12}]$ (entries 3 and 5–15). [b] CTAB was cetyltrimethylammonium bromide (0.27 mmol). [c] Isolated yields for benzoic acid, chromatographic yields for ArH. [d] $PdCl_2$ (0.024 mmol), PCy_3 (0.049 mmol). [e] Methyl formate (5 cm^3). [f] Concentration of PCPC was 0.012 mmol. [g] PCy_3 (0.036 mmol). [h] Ammonium formate: 19.5 (entry 13) and 4.0 (entry 14) mmol were added. [i] Ammonium formate (50.3 mmol). Methanol (3 cm^3) was used instead of methyl formate.

The presence of cetyltrimethylammonium bromide (CTAB), albeit not essential to the reaction, promoted carbonylation (*cf.* entries 10 and 11 and, even more dramatic, entries 7 and 8). The exact role played by the onium salt is not quite clear. It could enhance activation of methyl formate by PCPC in the same way as has been suggested in the catalytic synthesis of ethanol from methyl formate [13]. Stabilization of possible anionic catalytic species by CTAB may occur, or, simply, it may act as a surfactant with a transport role, moving the Pd catalytic species from the aqueous to the organic phase.

Dehalogenation took place to different degrees depending on the conditions, probably *via* hydrogenolysis since dihydrogen was produced *via* the water gas shift reaction (WGSR) or decomposition of formic acid.

$$CO + H_2O \rightleftharpoons H_2 + CO_2$$

$$HCOOCH_3 + H_2O \rightleftharpoons HCOOH + CH_3OH$$

$$HCOOH \longrightarrow CO_2 + H_2$$

The limited dehalogenation under such stringent conditions is surprising. It is known that aromatic chlorocompounds are easily converted to aromatic hydrocarbons under Pd catalysis in the presence of formates [14] or phosphines [15].

When we used ammonium formate dissolved in methanol (entry 15) instead of methyl formate, benzoic acid was obtained in low yield. Another run using both formates (entry 13) gave a considerable improvement in yield (35.8% *vs.* 18.2%). The promoting role of ammonium formate may be related to the known reaction involving aromatic bromides under CO [16].

$$ArBr + HCOOM + CO \xrightarrow{[PdCl_2(PPh_3)_2]} ArCOOH + MBr + CO \quad (1)$$

(M = alkali metal, ammonium, etc.). This reaction occurs only under CO. In the present procedure with ArCl, the required CO originates from methyl formate. The yield of benzoic acid apparently depends on the concentration of the formate salt (*cf.* entries 13 and 14) since the reaction shown above would predominate over simple hydroxycarbonylation of chlorobenzene [20]. Interestingly, the addition of ammonium formate led to a highly selective carbonylation reaction (*ca.* 100%). No dehalogenation to ArH was observed. Pri-Bar *et al.* [16] favoured a pathway involving nucleophilic attack of a formate ion on the palladium species ArCOPdX, giving formyl species ArCOPdOCHO. This would lead to a mixed formic anhydride whose decomposition would yield the acid [17*].

Under conditions of run 6, we examined other methyl formate-chloroarene reactions (Table 2). Substituted benzoic acids were obtained in all cases. In the carbonylation of chlorotoluenes and chlorophenols, *ortho*-substitution retarded the reaction. Chloroarenes substituted at the 3 and 4 positions were readily carbonylated to the corresponding aromatic acids in fair yields. Turnover frequencies (TFs) were quite reasonable for such difficult carbonylations (> 10) and higher than the TF of chlorobenzene itself under similar conditions. At variance with 3- and 4-chlorophenol, the *ortho*-substituted compound underwent extensive dechlorination leading to phenol, most of which, under the conditions employed (NaOH, CTAB) was *O*-alkylated to anisole [18]. With this sole exception, the reactions were highly selective.

TABLE 2. Methyl formate–chloroarene (ClArZ) reactions [a]

Chloroarene	Yields (%)		TF [b]	Σ [c] (%)
	ZArCOOH	ArZ		
2-OH	14.9	5.0 [d]	60	42
3-OH	27.8	4.0	110	85
4-OH	52.2	4.0	221	90
2-CH_3	10.3	0	37	100
3-CH_3	57.3	0	202	100
4-CH_3	> 35 [e]	0	– [e]	100
4-OCH_3	21.0	0	7.1	100
4-NO_2	65.5 [f]	– [f]	17.4	– [f]

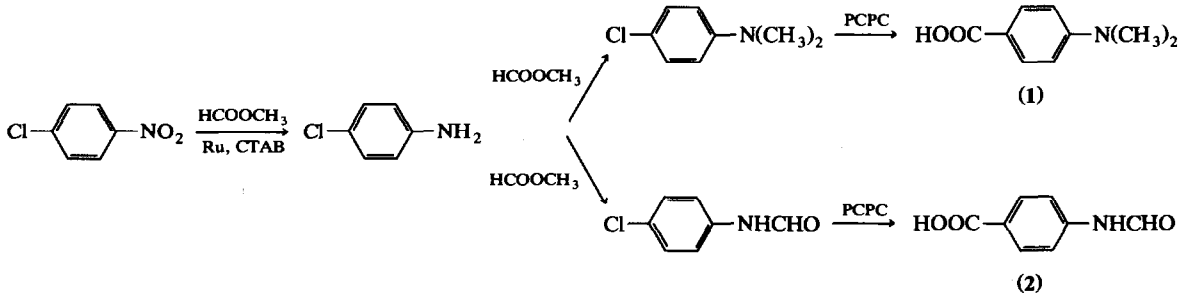
[a] Conditions were similar to those of run 6 in Table 1. [b] Mol ArCOOH mol Pd catalyst^{-1}. [c] Acid selectivity. [d] Anisol was also formed in 14% yield. [e] Isolated yield. In actual fact, the yield was higher (loss of product during work-up). [f] Z was either NHCHO or $N(CH_3)_2$ (see text). Other unidentified products were formed in low yield.

4-Chloronitrobenzene was said to be inert in the carbonylation reaction [7], but using the present procedure it was fully converted according to the following sequence (Scheme 1).

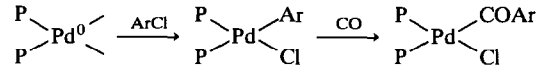
Two acids, **1** (7% yield) and **2** (58.2% yield), were formed. In the first step of the reactions, the nitro-group was reduced to 4-aminochlorobenzene and subsequently either methylated, leading to **1** [19] or acylated, leading to **2**. Once the dimethylamino or formamido group was incorporated, carbonylation took place. The predominance of **2** over **1** is probably due to the reaction temperature employed (160°C), too low to alkylate selectively the aminoarene [19].

The reaction demonstrates the potential of methyl formate, which reacts here simultaneously as a source of hydrogen and carbon monoxide and, in addition may serve as an alkylating agent.

It is generally agreed that the first step of the Pd-catalyzed aryl halide-carbonylation involves an ox-



Scheme 1.



Scheme 2.

$$[Pd(CO)L_2] + ArCl \xrightarrow{-L} [ArPd(Cl)(CO)L] \longrightarrow$$

$$[ArCOPd(Cl)L] \xrightarrow{H_2O/KOH} [ArCOPd(OH)L] \xrightarrow{+L} ArCOOH + [PdL_2]$$

Scheme 3.

idative addition of the C–X bond to a zerovalent Pd species, followed by very fast migratory insertion and nucleophilic cleavage [2] (Scheme 2). Oxidative addition is difficult in the case of chloroarenes. Thermal activation might help, but Pd^0 species must be stabilized by electron-rich and bulky phosphines. Tricyclohexylphosphine is sufficiently basic ($pK_a > 6.5$) and bulky (cone angle 179°) [6]. Under PCPC catalysis, the Pd complex exhibits high nucleophilicity and can be inserted into the C–Cl bond.

Once Pd^0 is formed from $[PdCl_2L_2]$, oxidative addition can take place. The oxidative addition is presumed to be rate-determining [20] whereas the carbonylation step is facile [6]. To keep Pd in its zero-valent state, the addition of PCy_3 to the Pd catalyst has been suggested [6]. However, in the present work this did not improve the yield of benzoic acid (entry 12).

We questioned the role of methyl formate. Obviously the formate ester provided the required carbon monoxide by ruthenium-catalyzed decarbonylation [8]. We replaced methyl formate by methanol (3 ml) and admitted CO (20 bar) under the conditions of run 5. Benzoic acid was formed in 11.2% yield (compared with 12.7%). Apparently, methyl formate is an equivalent of the CO/CH_3OH couple.

However, from the results of run 4, the ruthenium catalyst is not absolutly necessary. An alternative mechanism is activation of methyl formate by the palladium catalyst and strong basic ligands such as PCy_3 [21]. The activation of the formate ester by metal complexes has precedents with Mo [22], Ni [23], Co [24], and Ru [25]. Complexes of general formula $[M(CO)_nL_m]$ (L = phosphine) were obtained.

$$trans\text{-}[Mo(N_2)_2(dppe)_2] \xrightarrow{HCOOCH_3} [Mo(CO)(dppe)_2] \xrightarrow{HCOOCH_3} cis\text{-}[Mo(CO)_2(dppe)_2]$$

(dppe = $Ph_2PCH_2CH_2PPh_2$). In the presence of our palladium catalyst, activation could occur as shown in eqn. (2).

$$[PdCl_2L_2] \xrightarrow{HCOOCH_3} [Pd(CO)L_2] + CH_3OH \quad (2)$$

A possible intermediate might be $[Pd(PCy_3)_2]$ formed *in situ via* a route suggested by Heck [26].

$$[PdX_2L_2] + HCOOH \longrightarrow [PdL_2] + 2XH + CO_2 \quad (3)$$

HCOOH could stem from base-promoted hydrolysis of methyl formate. Oxidative addition of methyl formate to $[PdL_2]$ involving the C–H bond of the ester [27,28] would generate the active Pd^0 species.

$$[PdL_2] + HCOOCH_3 \longrightarrow [HPd(COOCH_3)L_2] \xrightarrow{-CH_3OH} [Pd(CO)L_2] \quad (4)$$

Ultimately, the acid would be formed *via* Scheme 3.

The effect of ammonium formate (HCOOM) could involve the Pd acyl species formed according to Scheme 2 or 3 [16,17*].

$$[ArCOPd(Cl)L] \xrightarrow[-MCl]{+HCOOM} [ArCOPd(L)OCHO] \longrightarrow ArCOOH + [PdL_2] + CO$$

4. Conclusion

Chloroarenes can be carbonylated to carboxylic acids with aqueous methyl formate and the binary mixture $[Ru_3(CO)_{12}]/[PdCl_2(PCy_3)_2]$. Ammonium formate greatly improves both the yield and the selectivity of the reaction. The main advantages of the formate method are adequate efficiency, no requirement for CO, and no addition of solvent. We are pursuing the possible extensions of these specific methyl formate reactions.

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References and notes

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