

Formation of Anhydrides by Homogeneous Palladium(II)-Catalyzed Carbonylation of Aryl Halides and Metal Carboxylates

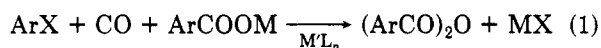
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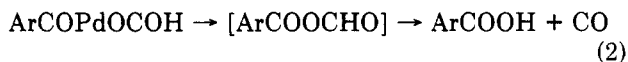
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Aryl iodides react with sodium, potassium, or calcium carboxylates and carbon monoxide in *N,N*-dimethylformamide, in the presence of palladium acetate, to give acid anhydrides. The reaction proceeds under mild conditions (50–90 °C, 2.7 atm), affording anhydrides in reasonable yields. The reaction is applicable to bromobenzene, provided one uses higher temperatures or adds tetrabutylammonium iodide. An acylpalladium carboxylate may be a key intermediate in these reactions.

Some classes of allylic compounds [e.g., chlorides, alcohols, ethers] are known to undergo palladium-catalyzed carbonylation at high pressure (125 atm), affording anhydrides in modest yields.² Sporadic reports have appeared in the patent literature on the preparation of benzoic anhydrides by metal-catalyzed carbonylation reactions (eq 1). However, yields of products are low, and



stringent reaction conditions are required.³ A possible reaction intermediate is an acylmetal carboxylate. An analogous intermediate has been invoked in the palladium-catalyzed formation of benzoic acids from aryl halides and formate salts under mild conditions (eq 2).⁴ The



stoichiometric transformation of palladium carboxylate complexes to give anhydrides was recently shown to occur under mild conditions.⁵

An investigation was made of the palladium(II)-catalyzed reaction of aryl halides with benzoic acid salts under low carbon monoxide pressures, in order to attain the synthesis of acid anhydrides under gentle conditions. Furthermore, this formation of anhydrides would provide evidence for the participation of anhydrides in the formate carbonylation reaction (eq 2) and on the reactivity of the acyl palladium intermediate involved in these transformations.

Results and Discussion

Treatment of iodobenzene with sodium benzoate, triphenylphosphine, and a catalytic quantity of palladium acetate in *N,N*-dimethylformamide, for 18 h at 90 °C and 2.7 atm of carbon monoxide, afforded benzoic anhydride in 65% yield. Pure anhydride was obtained by rapid extraction with ether and ice water. The ratio of iodobenzene to sodium benzoate to palladium(II) catalyst used was 10/15/1.0. Benzoic anhydride was also formed at atmospheric pressure; but the reaction is much slower.

Symmetrical anhydrides were synthesized in fair to good yields by reaction of a series of iodoarenes and sodium, potassium, or calcium carboxylates. The results are listed in Table I, with the product yield being determined on the anhydride itself, or by reaction of the latter with piperidine to give the piperidino amide. The amides were then analyzed by gas chromatography⁶ by comparison with authentic materials.

Table I. Yields of Anhydrides Obtained from Pd(OAc)₂-Catalyzed Carbonylation of Aryl Halides and Metal Carboxylates^a

entry	ArX	ArCOOM	yield of anhydride, ^b %
1	PhI	PhCO ₂ Na	65 (36)
2	PhI	PhCO ₂ K	51
3	PhI	(PhCO ₂) ₂ Ca ^c	71
4	PhBr	PhCO ₂ Na	2
5	PhBr	(PhCO ₂) ₂ Ca	15
6	PhI	4-CH ₃ C ₆ H ₄ CO ₂ Na	58 ^d
7	4-CH ₃ C ₆ H ₄ I	4-CH ₃ C ₆ H ₄ CO ₂ Na	63
8	4-CH ₃ OC ₆ H ₄ I	4-CH ₃ OC ₆ H ₄ CO ₂ Na	62
9	4-ClC ₆ H ₄ I	4-ClC ₆ H ₄ CO ₂ Na	38
10	4-O ₂ NC ₆ H ₄ I	4-O ₂ NC ₆ H ₄ CO ₂ Na	36
11	1-C ₁₀ H ₇ I	1-C ₁₀ H ₇ CO ₂ Na	77
12	sodium 2-iodobenzoate		(25)
13	1,2-diiodobenzene	PhCO ₂ Na	55 ^e
14	1,4-diiodobenzene	PhCO ₂ Na	(70) ^e

^a Conditions: palladium acetate (0.1 mmol), Ph₃P (0.3 mmol), ArX (1.0 mmol), ArCOOM (1.5 mmol), DMF (10 mL), CO (2.7 atm), 95 °C. ^b Yields by gas chromatography, except for those in parentheses which are isolated yields. ^c 0.75 mmol used in the calcium salt. ^d Combined yield of 4-CH₃OC₆H₄CONC₅H₁₀ (31%) and PhCONC₅H₁₀ (27%), resulting from amidation of the mixed anhydride as well as the two symmetrical anhydrides formed by in situ thermal disproportionation (Tedder, *J. M. Chem. Rev.* 1955, 55, 787). ^e Yield of diacid.

Anhydrides are formed in the presence of methyl, methoxy, chloro, and nitro substituents on the ring of the iodoarene. Lower product yields were realized when the substituent was electron-withdrawing, but the nucleophilicity of the substituted benzoate anion is also a factor. Also, the carbonylation of 1,2- and 1,4-diiodobenzenes (Table I, entries 13,14) is noteworthy as a mild route to diacids, which have recently been prepared by cobalt carbonyl catalyzed photocarbonylation in aqueous sodium hydroxide.⁷

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Table II. Influence of Solvent and Additives on the Pd(OAc)₂-Catalyzed Reaction of Iodobenzene or Bromobenzene with Sodium Benzoate^a

entry	ArX (concn, M)	solvent (polarity index) ^b	additive (concn, M)	% anhy- dride
1	PhI (1.0)	DMAC (6.5)		68
2	PhBr (1.0)	DMAC		4
3	PhBr (1.0)	DMAC		48 ^c
4	PhI (2.0)	DMF (6.4)		45
5	PhI (1.0)	DMF		65
6	PhI (0.5)	DMF		76
7	PhBr (1.0)	DMF		2
8	PhBr (1.0)	DMF	(C ₄ H ₉) ₄ N ⁺ I ⁻ (2.0)	30
9	PhI (1.0)	CH ₃ CN (5.8)		28
10	PhI (1.0)	THF (4.0)		27
11	PhI (1.0)	THF	Crown (20) ^d	70
12	PhI (1.0)	<i>t</i> -AmOH (2.7)		10

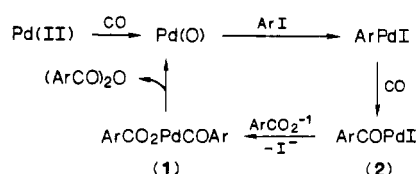
^a See footnote a of Table I (or the Experimental Section) for reaction conditions. ^b Snyder, L. R. *J. Chromatogr. Sci.* 1978, 16, 223. ^c Reaction temperature of 135 °C. ^d Dibenzo-18-crown-6.

The carbonylation reaction is sensitive to the nature of added phosphine. While benzoic anhydride was obtained in similar yield from iodobenzene and sodium benzoate with either triphenylphosphine (65%) or tri-*o*-tolylphosphine (63%), the use of the more basic trialkylphosphines (e.g. tri-*n*-butylphosphine, di-*n*-butylmethylphosphine) results in no anhydride formation. Benzoic anhydride was formed in 35% yield when the bidentate 1,2-bis[(bis(diphenylphosphino)]ethane was used as the added phosphine. Iodobenzene was recovered in 80% yield when the reaction was effected under nitrogen instead of carbon monoxide, with small amounts of biphenyl formed by a homocoupling reaction.

The influence of solvent, halide, and crown ether or quaternary ammonium salt on the conversion of halo-benzene, sodium benzoate, and carbon monoxide to benzoic anhydride was also examined, and the results are given in Table II. Only polar solvents such as DMF or *N,N*-dimethylacetamide (DMAC) facilitate reaction. Cation solvation plays a role in the reaction, as shown by the differences in reactivity of the calcium, sodium, and potassium benzoates (Table I, entries 1-3) as well as by the significant enhancement in yield attained by using tetrahydrofuran as the solvent in the presence of dibenzo-18-crown-6 (Table II, entries 10, 11). Poor yields of benzoic anhydride were realized by using bromobenzene as the reactant haloarene (Table I, entries 4, 5; Table II, entries 2, 7), except at elevated temperatures (Table II, entry 3), or when tetra-*n*-butylammonium iodide (Table II, entry 8) was present.

Solubility of the species in the reaction medium appears to be a factor at higher concentrations, i.e. a decrease in the molar concentration of iodobenzene leads to increased yields of anhydride (Table II, entries 4-6). A viscous suspension of the precipitating metal halide salt is formed at high concentrations, causing poor stirring and possibly a decrease in the solubility of carbon monoxide.

One can account for the results described above by the pathway outlined in Scheme I, assuming that the rate-determining step involves nucleophilic attack of the benzoate anion on a benzoylpalladium intermediate (1), itself formed by oxidative addition and carbon monoxide insertion. This scheme is consistent with the significant influence of the crown ether on the reaction, as well as the solvent effects, and the reduced nucleophilicity of the

Scheme I

benzoate anion when electron-withdrawing substituents are present. The retarding effect of basic trialkylphosphines can be attributed to the reduced electrophilicity of the palladium complex 2 in reaction with the benzoate salt.

The low reactivity of the aromatic bromides is surprising, given the facility for oxidative addition (ArI > ArBr >> ArCl)⁸ and the knowledge that bromoarenes experience oxidative addition and subsequent olefination,⁹ carbonylation,⁴ or hydrogen transfer¹⁰ under comparable, or even milder, conditions. Consequently, this low reactivity may not be a function of sluggish oxidative addition. This assumption is also supported by the decrease in yields found in reactions of iodoarenes bearing electron-withdrawing substituents [RC₆H₄I, R = 4-NO₂ < 4-Cl < 4-OCH₃ < H], a pattern that is opposite to that of the rate of oxidative addition.⁸

The low reactivity of aryl bromides may be due, in part, to the enhanced stability of an organopalladium bromide compared to a palladium iodide intermediate (2). In the platinum complexes, PtX(COPh)(PEt₃)₂, where X = Cl, Br, I, the iodo complex decomposed on heating while the chloro and bromo derivatives were quite stable and gave sharp melting points.¹¹ One way to overcome the low reactivity of the bromide substrate is to induce halogen exchange in the ArPdBr intermediate. Indeed, the addition of tetra-*n*-butylammonium iodide to the palladium acetate catalyzed reaction of bromobenzene increased the yields of anhydride from 2 to 30% (Table II).

In order to establish that the iodopalladium intermediate is more reactive than the analogous chloro complex, the carbonylation of iodobenzene was effected in the presence of tetrabutylammonium chloride. As a result of the exchange of chlorine for iodine ligands, no reaction occurs.

Experimental Section

Infrared spectra were recorded on a Perkin-Elmer 783 spectrometer. A Varian XL-300 spectrometer was used for nuclear magnetic resonance spectral determinations, and mass spectra were recorded on a VG-7070E spectrometer.

The aryl halides were purchased from commercial sources and were used as received. The benzoate salts, prepared from the corresponding acids, were dried at 100-140 °C prior to use. Solvents were dried by standard techniques. A glass pressure reaction vessel, containing a magnetic stirring bar, was used to carry out the reactions. Gas chromatographic analyses were performed on a Varian 3400 spectrometer equipped with an OV17 glass column. The anhydrides and the corresponding piperidino derivatives were characterized by infrared, nuclear magnetic resonance, and gas chromatography-mass spectrometry, in comparison with authentic materials. Standards of *N*-benzoylpiperidinyll amides were prepared by treating the acid chloride with piperidine in dry tetrahydrofuran.

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General Procedure for the Formation of Anhydrides. Palladium acetate (0.022 g, 0.10 mmol), triphenylphosphine (0.077 g, 0.30 mmol), and anhydrous sodium benzoate (0.216 g, 1.50 mmol) were placed in the reaction vessel. After the system was purged several times with carbon monoxide, a *N,N*-dimethylformamide (10 mL) solution containing the iodoarene (1.0 mmol) and biphenyl (internal standard) was added. The reaction vessel was then pressurized to 2.7 atm with carbon monoxide. The reaction mixture was heated to 95 °C for 18 h, during which time the color of the solution changed from yellow to deep violet (no precipitate was formed). The reaction mixture was cooled to room temperature, and the vessel was opened under a nitrogen atmosphere. Pure anhydride was obtained by rapid ether extraction of the DMF solution (the latter having been treated with ice-cold aqueous sodium chloride), followed by column chromatography through a short silica gel column.

In order to isolate the benzoylpiperidine, piperidine (0.25 g, 3.0 mmol) was added, followed by tetrahydrofuran (10 mL), and the reaction mixture was stirred overnight at room temperature. Dilute hydrochloric acid was added, and the mixture was extracted with ether. The ether extract was washed with a saturated solution of sodium carbonate, dried (MgSO_4), and concentrated to give the pure *N*-aroylpiperidine.

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Registry No. PhI, 591-50-4; PhBr, 108-86-1; 4- $\text{CH}_3\text{C}_6\text{H}_4\text{I}$, 624-31-7; 4- $\text{CH}_3\text{OC}_6\text{H}_4\text{I}$, 696-62-8; 4- $\text{ClC}_6\text{H}_4\text{I}$, 637-87-6; 4- $\text{O}_2\text{NC}_6\text{H}_4\text{I}$, 636-98-6; 1- $\text{C}_{10}\text{H}_7\text{I}$, 90-14-2; PhCO_2Na , 532-32-1; PhCO_2K , 582-25-2; $(\text{PhCO}_2)_2\text{C}_9$, 2090-05-3; 4- $\text{CH}_3\text{C}_6\text{H}_4\text{CO}_2\text{Na}$, 17264-54-9; 4- $\text{O}_2\text{NC}_6\text{H}_4\text{CO}_2\text{Na}$, 3847-57-2; 4- $\text{CH}_3\text{OC}_6\text{H}_4\text{CO}_2\text{Na}$, 536-45-8; 4- $\text{ClC}_6\text{H}_4\text{CO}_2\text{Na}$, 3686-66-6; 1- $\text{C}_{10}\text{H}_7\text{CO}_2\text{Na}$, 17273-44-8; Ph_3P , 603-35-0; 4- $\text{CH}_3\text{OC}_6\text{H}_4\text{CONC}_5\text{H}_{10}$, 57700-94-4; $\text{PhCONC}_5\text{H}_{10}$, 776-75-0; $(\text{C}_4\text{H}_9)_4\text{N}^+\text{I}^-$, 311-28-4; benzoic anhydride, 93-97-0; 4-methylbenzoic anhydride, 13222-85-0, 4-methoxybenzoic anhydride, 794-94-5; 4-chlorobenzoic anhydride, 790-41-0; 4-nitrobenzoic anhydride, 902-47-6; 1-naphthalene carboxylic anhydride, 64985-86-0; 1,2-benzenedicarboxylic acid, 88-99-3; 1,4-benzenedicarboxylic acid, 100-21-0; palladium acetate, 3375-31-3; sodium 2-iodobenzoate, 2532-17-4; 1,2-diiodobenzene, 615-42-9; 1,4-diiodobenzene, 624-38-4; dibenzo-18-crown-6, 14098-24-9; tri-*o*-tolylphosphine, 1038-95-5; 1,2-bis[bis(diphenylphosphino)]ethane, 1663-45-2; phthalic anhydride, 85-44-9.

Manganese(III)-Based Oxidative Free-Radical Cyclizations.¹ Oxidative Cyclization and Aromatization of 3-Oxo-6-heptenoate Esters

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Treatment of 3-oxo-6-heptenoate esters **1**, **2**, **4**–**15** with 4 equiv of $\text{Mn}(\text{OAc})_3 \cdot 2\text{H}_2\text{O}$ and 1 equiv of $\text{Cu}(\text{OAc})_2 \cdot \text{H}_2\text{O}$ gave salicylate esters **16**–**29** in yields of 17–78%. Similar treatment with 4 equiv of $\text{Mn}(\text{OAc})_3 \cdot 2\text{H}_2\text{O}$ and excess LiCl gave mixtures of salicylate esters and chlorides such as **45** and **46**, which could be converted to the salicylate ester by heating at reflux in acetic acid containing excess LiCl in overall yields of 40–90%. Treatment of α -chloro β -keto ester **3** with 2 equiv of $\text{Mn}(\text{OAc})_3 \cdot 2\text{H}_2\text{O}$ and 1 equiv of $\text{Cu}(\text{OAc})_2 \cdot \text{H}_2\text{O}$ gave a mixture of salicylate **17** and methylenecyclohexane **41**. Treatment of δ -hydroxy β -keto esters **51a** and **51b** with 2 equiv of $\text{Mn}(\text{OAc})_3 \cdot 2\text{H}_2\text{O}$ gave epoxides **53a** and **53b** in 50% and 30% yield, respectively.

Introduction

We have recently reported that oxidative cyclization of β -keto ester **1** with 4 equiv of $\text{Mn}(\text{OAc})_3 \cdot 2\text{H}_2\text{O}$ ³ and 1 equiv of $\text{Cu}(\text{OAc})_2 \cdot \text{H}_2\text{O}$ gave methyl salicylate (**16**) in 77% yield as shown in Table I.^{1c,4} Since β -keto esters such as **1** are readily available by alkylation of the dianion of methyl acetoacetate,⁵ this procedure appeared to offer a novel and general method for the preparation of salicylate derivatives.⁶ We report here studies indicating the scope and limitations of this oxidative cyclization procedure.

The detailed steps involved in the conversion of β -keto ester **1** to salicylate **16** can be surmised based on cycliza-

tions of related β -keto esters that do not give aromatic products.¹ Presumably, the β -keto ester of **1** forms a manganese enolate, which interacts with the double bond to give the cyclic radical **30** as a reactive intermediate.^{1d} The enol radical is not a plausible intermediate since we have shown that the double bond is involved in the rate-determining step of the oxidation of β -keto esters containing two hydrogens on the α -carbon. Secondary radicals react with cupric acetate to give copper(III) intermediates, which undergo oxidative β -hydride elimination to give alkenes and cuprous acetate.⁷ The radical of **30** should react with cupric acetate to give **31** as a mixture of double-bond isomers. The cuprous acetate produced in this oxidation is reoxidized by a second equivalent of $\text{Mn}(\text{OAc})_3 \cdot 2\text{H}_2\text{O}$; however, neither isomer of **31** can be isolated, even when a deficiency of $\text{Mn}(\text{OAc})_3 \cdot 2\text{H}_2\text{O}$ is used. Presumably, β -keto ester **31** is converted to the manganese enolate, which is oxidized to the enol radical. Oxidative β -hydride elimination will give the cyclohexadienone,

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