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Notes

Dechlorination of Aryl Chlorides with Sodium Formate Using a Homogeneous Palladium Catalyst

Margaret E. Logan* and Mark E. Oinen

Department of Chemistry, SUNY College at Brockport, Brockport, New York 14420

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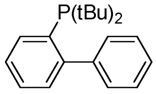
Summary: The dechlorination of substituted aryl chlorides using a homogeneous palladium catalyst system and sodium formate in refluxing methanol is described. The catalyst was formed in situ from the air-stable precursors 2-(di-tert-butylphosphino)-biphenyl and Pd(OAc)$_2$. The reaction conditions were successful for a range of aryl chlorides with activating and deactivating groups at a position para to the chloride. The reactions gave high yields (90−98%) of the product of reduction within several hours.

Introduction

There has been an explosion of chemistry over the past 20 years using aryl bromides and iodides in homogeneous palladium-catalyzed coupling reactions with organometallic compounds, as well as with oxygen- and nitrogen-containing nucleophiles.[1] Analogous chemistry using aryl chlorides has come more slowly, due to the strength of the C−Cl bond relative to those of the C−Br and C−I bonds.[2] However, recently new ligands for palladium, including many that are air-stable, have given homogeneous palladium catalysts that readily react with aryl chlorides in the coupling reactions described above under comparatively mild conditions with reduced byproduct formation.[3] The need for improved methods to remediate materials that are contaminated with polychlorinated biphenyls (PCB's) and dioxins has provided a compelling rationale for exploring the reduction of aryl chlorides using homogeneous palladium catalysis and these newer ligands under mild conditions.[4]

At the time that this work was begun, the use of homogeneous palladium catalysts for the hydrodechlorination of aryl chlorides had been demonstrated with several different ligands and palladium sources, with evidence of increasing interest in this area of chemistry.[3a,5] However, many of these methods employed ligands that are not air-stable and commercially available, required temperatures of up to 150 °C for electron-rich aryl halides, used strong bases such as sodium *tert*-butoxide, or were performed on a very limited number of substrates. In addition, despite the growing interest in systems for dehydrohalogenation of aryl chlorides, the use of Buchwald biphenyl ligands such as **1** in palladium-catalyzed hydrodechlorination had not been described. The fact that their utility in other reactions of aryl chlorides, such as Suzuki−Miyaura coupling and amination, had been clearly demonstrated,[6] studies of the catalyst lifetime had been performed,[7] and systematic studies of the impact of structural variation of the biaryl substituents were underway,[8] made them particularly attractive. In addition, because the Buchwald ligands have been used in aqueous systems[3e] and have functionality that has been used for immobilization without loss of catalytic activity,[9] they also offered a fit with our longer term interest in the development of reduction systems that use ligands immobilized on a solid support in an aqueous environment. However, it was important to first establish that these ligands were effective in the reduction of simple aryl chlorides. In this paper we describe the efficient reduction of aryl chlorides with sodium formate in refluxing methanol in the presence of the



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* To whom correspondence should be addressed. Fax: 585-395-5805. E-mail: mlogan@brockport.edu.

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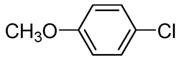
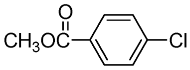
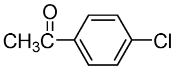
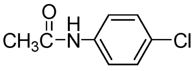
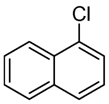
Table 1. Hydrodechlorination of Aryl Chlorides by Eq 1

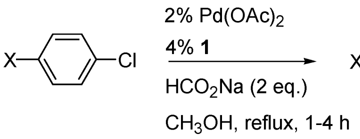
Entry	Aryl Chloride	Time, h[a]	Yield, %[b]
1		3	99
2		1.5	97
3		2	100
4		3	97 (89)
5		4	95 (90)

[a] Average of two runs. [b] GC yields, average of two runs (isolated yields).

homogeneous palladium(0) catalyst formed from palladium(II) acetate and the ligand 2-(di-*tert*-butylphosphino)biphenyl (**1**).

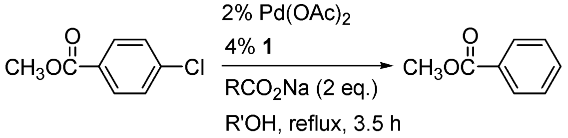
Results and Discussion

We examined the reduction of a series of aryl chlorides in refluxing methanol under argon, using 2 equiv of sodium formate as the hydride source, 2 mol % of $Pd(OAc)_2$, and 4 mol % of the biphenyl ligand **1** (eq 1). The results are compiled in Table 1. The combination of $Pd(OAc)_2$ and ligand **1** was attractive, because both the Pd source and ligand are air-stable and are commercially available. The reaction conditions chosen were used previously with the air-sensitive chelating phosphine ligand 1,3-bis(diisopropylphosphino)propane (DIPPP), where the use of either sodium methoxide or sodium formate as a hydride source in methanol was found to be effective.[5b] Hydrodechlorination in the presence of ligand **1** occurred at lower temperatures and in shorter reaction times as compared to those observed when DIPPP was used: with ligand **1**, hydrodechlorination was observed at reflux in methanol, rather than requiring a higher temperature and sealed reaction vessels, as was found with DIPPP. In addition, the low basicity of the formate ion allowed the reaction to proceed under nearly neutral conditions. No measures were taken to dry the sodium formate; thus, it is likely that water was present in the reaction mixture, with no untoward consequences.



(1)

Table 2. The Hydride Source in Hydrodechlorination



R	R′	% conversion[a]
CH_3	CH_3	5
H	$(CH_3)_3C$	90
H	CH_3	97[b]

[a] GC yield. [b] 1.5 h reaction time, from Table 1.

The aryl chloride starting materials consisted of four phenyl chlorides having para substituents with a range of electronic characteristics, as well as 1-chloronaphthalene (Table 1). The reactions were monitored by gas chromatography using an internal standard, with the retention time of products compared to those of authentic materials. The percent reduction of aryl chloride was excellent, with no apparent formation of byproducts. In all cases, the reactions were complete within 4 h, although there was some variability across runs. Reaction times were more consistent when $Pd(OAc)_2$ and **1** were stirred in a portion of the methanol solvent for 5 min prior to the addition of the aryl chloride and remaining methanol. Entries 1 and 4, in which the aryl chlorides have electron-donating substituents, reacted nearly as quickly as aryl chlorides having electron-withdrawing groups, still in refluxing methanol. For entries 4 and 5, the products were easily isolated by an aqueous workup followed by purification by filtration through silica gel. The isolated yields were high, consistent with the quantitative hydrodechlorination and absence of byproducts observed by GC.

Sodium formate, rather than methanol, is the hydride source in these reactions, although both are mechanistically plausible.[5b] This was established by performing the hydrodechlorination under two additional sets of conditions and comparing them with the percent conversions obtained under the “standard conditions” (Table 2). In one case the reaction was performed with sodium formate as the base and *tert*-butyl alcohol as the solvent, while in the other it was performed with sodium acetate as the base and methanol as the solvent. At 1.5 h, the reaction with formate ion in *tert*-butyl alcohol was at 90% conversion, which was similar to the control reaction with formate in methanol, while the reaction with sodium acetate in methanol had proceeded to only 5% conversion.

The ease with which the hydrodechlorination of a range of aryl chlorides occurs according to eq 1 bodes well for the possibility of hydrodechlorination of PCB’s and dioxins under mild conditions, particularly given the continuing, rapid development of Pd(0)/catalyst systems with even greater reactivity.

Experimental Section

General Procedures. All chemical reactions were performed under argon. Syringes were used for transferring liquids. 1-Butanol and *tert*-butyl alcohol were degassed with a stream of Ar bubbles during sonication. Anhydrous, deoxygenated methanol was used as received, as were all other chemicals. 2-(Di-*tert*-butylphosphino)-biphenyl was purchased from Strem. Silica gel (60−200 mesh) was used. GC analysis was performed on a 15 m × 0.32 mm × 0.25 μM dimethyl polysiloxane column.

Hydrodechlorination. An oven-dried 25 mL two-neck round-bottom flask with magnetic stir bar was equipped with a rubber septum and a ground-glass stopper. For the reduction of 2 mmol of aryl chloride, $Pd(OAc)_2$ (2 mol %) and 2-(di-*tert*-butylphosphino)biphenyl (4 mol %) were added, followed by sodium formate (4 mmol). The apparatus was put under argon. Methanol (1 mL) was added through the septum, and the reaction mixture was stirred for 5 min prior to addition of the aryl chloride (2 mmol). The aryl chloride was added by syringe if it was a liquid. If the aryl chloride was a solid, it was added quickly through the neck of the flask. A second portion of methanol (1 mL) was added. In examples in which the yield was monitored by GC using an internal standard, 1-butanol (0.090 mL) was added via syringe. The reaction mixture was heated at reflux, and reaction progress was monitored by GC, with or without an internal standard. In a specific example, the general procedure was used with Pd(OAc)$_2$ (9.2 mg, 0.041 mmol), 2-(di-*tert*-butylphosphino)biphenyl (25.2 mg, 0.084 mmol), sodium formate (0.274 g, 4.0 mmol), and 1-chloroacetanilide (0.328 g, 1.9 mmol).

GC Standardization. A 2 mL volumetric flask was tared. To the tared flask was added the aryl chloride starting material, authentic product, and 1-butanol. Liquids were added using a 0.050 mL syringe. Solids were added, using between 0.050 and 0.060 g. The flask was weighed after the addition of each compound on a laboratory scale (±0.001 g). After all three compounds were added to the flask, it was filled to 2 mL with dry methanol. The mixture was shaken to dissolve the solids and promote mixing. In some cases the flask was sonicated to dissolve solids. The sample was analyzed by GC in the following manner: a sample (~1 μL) was taken from the volumetric flask and injected. The temperature was ramped from 40 °C at a rate of 5 °C/min until the column was at a temperature appropriate for eluting the compound with the longest retention time. The resulting peaks were integrated. This process was repeated five times, and the areas were used to calculate the response ratio of the starting material to 1-butanol and of the product to 1-butanol. The response ratios used to determine yields were an average of the response ratios calculated for the five trials.

GC Analysis of Reactions. At time intervals, a small portion of the reaction mixture was removed by pipet (~0.025 mL) and flushed from the pipet with HPLC grade methanol (~0.5 mL). Approximately 1 μL was injected into the GC, and the resulting peaks were integrated. The identities of the compounds present were confirmed by comparison with retention times from the standard GC data. Yields were determined using the 1-butanol as an internal standard.

Product Isolation and Purification. Upon completion of the reaction the contents of the reaction flask were transferred using EtOAc (2 × 5 mL). The EtOAc washes were vacuum-filtered through diatomaceous earth (3 mL) in a 15 mL fritted funnel, and the diatomaceous earth was washed with EtOAc (5 mL). The filtrate was washed with water (10 mL), and the water layer was back-extracted twice with EtOAc (2 × 5 mL). The combined extracts were washed with saturated NaCl solution (10 mL) and dried over anhydrous Na$_2$SO$_4$. The EtOAc was removed under reduced pressure to yield the crude product. The crude product was chromatographed on silica gel (10 mL). The desired fractions were combined, and solvent was removed under reduced pressure to yield purified product. The product identity was confirmed by GC and ^{1}H NMR by comparison with authentic material, and purity was determined by ^{1}H NMR.

Hydrodechlorination in Methanol in the Presence of Sodium Acetate. The general procedure was followed, using sodium acetate in place of sodium formate, and the following quantities: Pd(OAc)$_2$ (9.1 mg, 0.040 mmol), 2-(di-*tert*-butylphosphino)biphenyl (25.8 mg, 0.086 mmol), sodium acetate (0.330 g, 4.0 mmol), methyl 4-chlorobenzoate (0.366 g, 2.1 mmol), and methanol (2 mL). The reaction was monitored by GC, from which the percent conversion was determined using the response factors.

Hydrodechlorination in *tert*-Butyl Alcohol in the Presence of Sodium Formate. The general procedure was followed, using *tert*-butyl alcohol in place of methanol, and the following quantities: Pd(OAc)$_2$ (9.4 mg, 0.042 mmol), 2-(di-*tert*-butylphosphino)biphenyl (25.2 mg (0.084 mmol), sodium formate (0.285 g, 4.2 mmol), methyl 4-chlorobenzoate (0.342 g, 2.1 mmol), and *tert*-butyl alcohol (1 mL). The reaction was monitored by GC, from which the percent conversion was determined using the response factors.

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