# Microwave-Promoted Hydroxycarbonylation in Water Using Gaseous Carbon Monoxide and Pre-Pressurized Reaction Vessels

Chad M. Kormos, Nicholas E. Leadbeater\*

Department of Chemistry, University of Connecticut, 55 North Eagleville Road, Storrs, CT 06269-3060, USA Fax +1(860)4862981; E-mail: nicholas.leadbeater@uconn.edu *Received 23 March 2006* 

**Abstract:** The microwave-promoted hydroxycarbonylation of aryl iodides using reaction vessels pre-pressurized with CO is reported. Reactions are performed using simple palladium salts with loadings of either 0.01 mol% or 1 mol%.

Key words: palladium, carbonylations, catalysis, water, microwave

Microwave-promoted synthesis is an area of increasing interest in both academic and industrial laboratories.<sup>1–3</sup> As well as being energy-efficient,<sup>4</sup> microwave heating can also enhance the rate of reactions and in many cases improve product yields. Also, as the field matures, people are finding that they can perform chemistry using microwave heating that cannot be achieved using 'convention-al' heating methods, thus opening up new avenues for synthesis.

Our interest has recently turned to the concept of performing microwave-promoted chemistry in vessels that have been pre-pressurized with reactive gases. This would broaden the application of microwave promoted synthesis. It is difficult to preload commercially available microwave tubes with a gas. In addition, most commercially available single-mode microwave systems have a pressure limit of 20-30 bar. With the combination of a pressure of reactive gas and the autogenic pressure of solvents at elevated temperatures, there is a limit to the temperature to which reaction mixtures can be heated. These factors have been reflected in the scarcity of reports of organic synthesis in pre-pressurized vessels using microwave heating.<sup>5–7</sup> Using a newly developed dedicated multimode microwave reactor (Anton Paar Synthos 3000) it is possible to perform reactions in heavy-walled quartz reaction vessels with operating limits of 80 bar.<sup>8</sup> The reactor is also equipped with a gas-loading interface, allowing the vessels to be pre-pressurized to up to 20 bar prior to placing in the microwave cavity.<sup>9</sup> The use of this apparatus in the Diels-Alder reaction under an atmosphere of ethene has been reported.<sup>7</sup>

Palladium-mediated carbonylation chemistry is an important tool in the synthetic chemist's portfolio.<sup>10,11</sup> When transferring this chemistry from conventional to microwave heating a number of approaches have been devel-

SYNLETT 2006, No. 11, pp 1663–1666 Advanced online publication: 04.07.2006 DOI: 10.1055/s-2006-944216; Art ID: S04306ST © Georg Thieme Verlag Stuttgart · New York oped to circumvent the problem of working with gaseous carbon monoxide.<sup>12</sup> Larhed and co-workers have developed and elegantly exploited the use of  $Mo(CO)_6$  as a source of carbon monoxide in conjunction with microwave heating.<sup>13</sup> Advantages of using  $Mo(CO)_6$  as a replacement for gaseous CO include the fact that it is a solid and is easily used on a small scale with commercially available monomode microwave apparatus with no modification required. However, Mo(CO)<sub>6</sub> is toxic and its use results in metal waste; this being a particular problem if the reaction is to be scaled up. We wanted to develop an alternative strategy based around using gaseous carbon monoxide in conjunction with the gas-loading capability of the Synthos 3000. Since much of the chemistry we have focused our attention on has been performed using water as a solvent,<sup>14</sup> we wanted first to study the palladiummediated hydroxycarbonylation of aryl halides in water, forming the corresponding benzoic acids. This transformation has been reported previously using conventional heating.<sup>15</sup> The authors note that the reaction is very efficient; a turnover number of 100,000 being reported for 4iodobenzoic acid holding the reaction mixture at 80 °C for six days. Other approaches to hydroxylcarbonylation have involved using phosphine-ligated palladium catalysts<sup>16,17</sup> or ionic liquids as solvents (Scheme 1).<sup>18</sup>



Scheme 1

Our starting point was to use reaction conditions similar to those developed for the Suzuki coupling in water; namely using ligandless palladium sources as catalysts, sodium carbonate (3.7 equiv) as a base and tetrabutylammonium bromide (TBAB) as a phase-transfer agent.<sup>19–21</sup> Preloading reaction vessels to 14 bar with CO, we screened a range of conditions for the conversion of 4-iodoanisole to 4-methoxybenzoic acid (anisic acid). Key results are shown in Table 1. Palladium acetate proved to be a good catalyst for the reaction and as a starting point we used 1 mol%. We found that the reaction worked better in the absence of a phase-transfer agent (Table 1, entries 1 and 2). A reaction temperature of 165 °C is optimal; increasing this temperature has no effect on product yield (Table 1, entry 3). Reduction of the base by half has a deleterious effect on the product yield (Table 1, entry 4). Using Herrmann's palladacycle<sup>22</sup> instead of palladium acetate offered no advantage in terms of product yield (Table 1, entry 5). Since in our Suzuki protocol we showed that very low catalyst loadings could be used,<sup>19</sup> we decided to examine the effect of reducing catalyst loading in the carbonylation reaction. When working in water, a major problem can be precipitation of palladium from a stock solution, particularly when working with a salt such as palladium acetate. This is avoided by using an acid stabilized stock solution such as that purchased as an ICP standard for palladium. This can be diluted accordingly to give solutions of the desired concentrations. Using this, we found that the catalyst loading can be decreased to 0.01 mol% with a 14% decrease in product yield (Table 1, entries 6 and 7). No starting material remained at the end of the reaction hence extension of reaction time to improve product yields would have no effect. Moving to catalyst loadings lower that 0.01 mol% had a significant detrimental effect (Table 1, entries 8 and 9).

 Table 1
 Optimization of Conditions for the Hydroxycarbonylation

 Reaction
 Provide the Hydroxycarbonylation

MeO	[Pd], base, H <sub>2</sub> O MeO	ОН
Entry	Reaction conditions <sup>a,b</sup>	Yield (%)
1	1 mol% Pd(OAc) <sub>2</sub> , 3.7 equiv Na <sub>2</sub> CO <sub>3</sub> , 1 equiv TBAB, 165 °C, 20 min	65
2	1 mol% Pd(OAc) <sub>2</sub> , 3.7 equiv Na <sub>2</sub> CO <sub>3</sub> , <b>no TBAB</b> , 165 °C, 20 min	86
3	1 mol% Pd(OAc) <sub>2</sub> , 3.7 equiv Na <sub>2</sub> CO <sub>3</sub> , <b>no TBAB</b> , <b>200</b> °C, 20 min	80
4	1 mol% Pd(OAc) <sub>2</sub> , <b>1.9 equiv Na<sub>2</sub>CO<sub>3</sub></b> , <b>no TBAB</b> , 165 °C, 20 min	67
5	1 mol% Herrmann's palladacycle, 3.7 equiv Na <sub>2</sub> CO <sub>3</sub> , <b>no TBAB</b> , 165 °C, 20 min	87
6	<b>0.1 mol% Pd soln</b> , 3.7 equiv Na <sub>2</sub> CO <sub>3</sub> , <b>no TBAB</b> , 165 °C, 20 min	72
7	<b>0.01 mol% Pd soln</b> , 3.7 equiv Na <sub>2</sub> CO <sub>3</sub> , <b>no TBAB</b> , 165 °C, 20 min	70
8	<b>0.001 mol% Pd soln</b> , 3.7 equiv Na <sub>2</sub> CO <sub>3</sub> , <b>no TBAB</b> , 165 °C, 20 min	64
9	<b>0.0001 mol% Pd soln</b> , 3.7 equiv Na <sub>2</sub> CO <sub>3</sub> , <b>no TBAB</b> , 165 °C, 20 min	52

<sup>&</sup>lt;sup>a</sup> Reactions were run in a sealed tube, preloaded with 14 bar CO, using 2 mmol 4-iodoanisole and 10 mL  $H_2O$ . An initial microwave irradiation power of 1000 W was used, the temperature being ramped from r.t. to that shown.

<sup>b</sup> For clarity, changes in reaction conditions from entry 1 are noted in bold.

We decided to screen a range of substrates in the reaction using both 1 mol%  $Pd(OAc)_2$  and 0.01 mol% palladium derived from our ICP standard. The results are shown in Table 2. Only aryl iodides can be coupled using the methodology; aryl bromides are unreactive (Table 2, entry 2).

Table 2 Hydroxycarbonylation of Aryl Halides in Water<sup>a</sup>

R	MW, CO [Pd], Na <sub>2</sub> CO <sub>3</sub> , H <sub>2</sub> O	→ R	ОН
Entry	Aryl halide	Product yield	0.01% Pd soln
1	OMe	86	72
2	OMe	0	0
3	Me	69	80
4	COMe	82	59
5		92	80
6	CF <sub>3</sub>	59	_
7	NO <sub>2</sub>	54	_
8	NH <sub>2</sub>	60	-
9	F	77	70
10	Me	70	74
11	MeO	68	63
12		15	_

<sup>&</sup>lt;sup>a</sup> Reactions were run in a sealed tube, preloaded with 14 bar CO, using 2 mmol aryl halide, 7.4 mmol Na<sub>2</sub>CO<sub>3</sub>, and 10 mL H<sub>2</sub>O. An initial microwave irradiation power of 800 W was used, the temperature being ramped from r.t. to 165 °C and held until a total reaction time of 20 min had elapsed.

A range of aryl iodides can be converted to the benzoic acids including *ortho*-substituted examples (Table 2, entries 10 and 11). Generally, product yields are higher when using the higher catalyst loading, the exceptions being 2- and 4-iodotoluene (Table 2, entries 3 and 10). We find that a representative heteroaromatic substrate gives only moderate yields of the desired product (Table 2, entry 12). This is attributed in part to competitive decomposition as well as to the difficulty in isolating the acid product from the reaction mixture.

In summary, we have presented here a methodology for the microwave-promoted hydroxycarbonylation of aryl iodides using reaction vessels pre-pressurized with CO. It offers an alternative to using solid CO sources. A concern about using carbon monoxide gas in microwave vessels has been the issue of leakage. Here we show that, with the proper apparatus, the use of carbon monoxide gas is quick, easy, and safe.

#### **Description of the Microwave Apparatus**

A commercially available multimode microwave unit was used for the reactions. The instrument is equipped with two magnetrons with combined continuous microwave output power from 0 to 1400 W. Heavy-walled quartz reaction vessels (80 mL capacity, up to 60 mL working volume) were used. These vessels are dedicated for reactions at high pressure (up to 80 bar). The quartz vessels were capped with special seals and a protective PEEK cap and then were placed inside protecting air-cooling jackets made of PEEK. The seals comprise a release valve that could be manually operated. The individual vessels were placed in an eight-position rotor and fixed in place by screwing down the upper rotor plate, and the rotor was finally closed with a protective hood. The vessels, once placed and secured in the rotor with the hood attached, were loaded with carbon monoxide using a commercially available gas-loading kit, access being via a bayonet link. They were pressurized directly from a carbon monoxide cylinder to 14 bar (ca. 200 psi). The rotor was then placed into the microwave cavity. The temperature was monitored using an internal gas balloon thermometer placed in one reference vessel and additionally by exterior IR thermography. Pressure was monitored by a simultaneous hydraulic pressure-sensing device for all vessels, with recording of the highest pressure level and pressure increase. Reaction vessels were stirred by means of a rotating magnetic plate located below the floor of the microwave cavity and a Teflon-coated magnetic stir bar in the vessel. At the end of a reaction, any remaining pressure was vented by releasing the venting screw on each reaction vessel whilst still in the rotor access being via frontal holes in the rotor lid.

### Typical Procedure for the Hydroxycarbonylation of 4-Iodoanisole.

In an 80 mL quartz tube was placed 4-iodoanisole (468 mg, 2.0 mmol),  $Na_2CO_3$  (0.785 g, 7.4 mmol),  $Pd(OAc)_2$  (4.5 mg, 0.02 mmol, 1 mol%) and  $H_2O$  (10 mL). The vessel was sealed and loaded onto the rotor. Three other vessels were prepared similarly. Each vessel was pressurized to 14 bar with CO. The loaded rotor was subjected to a maximum of 1000 W microwave power in a ramp to 165 °C and then held at this temperature until a total reaction time of 20 min had elapsed. The reaction mixture was stirred continuously and the pressure peaked at approximately 30 bar. Upon completion, the reaction vessels were allowed to cool to 50 °C, this taking around 20 min. Any remaining pressure was vented in a fume cupboard and then the vessels were removed from the rotor. The contents acidified with HCl to pH 1–3. The aqueous solution was

extracted with Et<sub>2</sub>O (3 × 15 mL). The organic washings were combined, dried over MgSO<sub>4</sub> and the Et<sub>2</sub>O removed on a rotary evaporator. This left the crude product, which was isolated and yield determined by NMR spectroscopy using an internal standard. Product characterization was by comparison of NMR data with that in the literature.

## Acknowledgment

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