

Application of a Batch Microwave Unit for Scale-Up of Alkoxy carbonylation Reactions Using a Near-Stoichiometric Loading of Carbon Monoxide

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Abstract:

The ethoxycarbonylation of iodobenzene was performed on the 1 mol scale in batch mode using microwave heating. The reaction was performed using both an excess and a near stoichiometric loading of carbon monoxide, comparable yields being obtained. Six different alkoxy carbonylation reactions were then performed simultaneously on the 50 mmol scale using a near-stoichiometric loading of carbon monoxide with excellent conversions in each case.

1. Introduction

Palladium-catalyzed carbonylation of aryl halides offers a one-step route to a range of products including carboxylic acids, esters, and amides.^{1,2} Of these variants, alkoxy carbonylation (synthesis of esters) accounts for the majority of the industrial applications. In our laboratory we have been focusing attention on the use of simple ligandless palladium complexes as catalysts for carbonylation chemistry.³ We perform our reactions using microwave heating, this being a valuable tool for synthetic chemists because it is possible to enhance the rate of reactions and, in many cases, improve product yields.⁴ Larhed and co-workers have used Mo(CO)₆ as a source of carbon monoxide for the preparation of amides, esters, and carboxylic acids from aryl halides using microwave heating.⁵ 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 microwave apparatus with no modification required. However, Mo(CO)₆ is expensive and toxic, and its use results in metal waste—this being a particular problem if the reaction is to be scaled up. We have found that it is possible to perform alkoxy carbonylation reactions of aryl iodides in reaction vessels

prepressurized with carbon monoxide.⁶ Reactions were performed using 0.1 mol % palladium acetate as catalyst with no additional ligand required. DBU proved to be the optimal base for the reaction, and a range of aryl iodide substrates can be converted to the corresponding esters using this methodology. Reactions were complete within 20 min at 125 °C. We subsequently developed a methodology for performing the reaction using a near-stoichiometric loading of carbon monoxide.⁷ We loaded the reaction vessel with the requisite quantity of carbon monoxide and then used nitrogen to reach a total pressure of 10 bar. We had to increase the palladium loading to 0.5 mol % to obtain good yields of the desired ester products. Reactions were again complete within 20 min at 125 °C.

Recently we have become interested in developing scale-up strategies for microwave-promoted reactions. This is essential if the technique is going to continue to gain acceptance and become practical at the process level. Possible approaches to scale-up include both batch and continuous-flow processing. Recent work in our laboratory and others has been focused on exploring both possibilities.^{8–10} For part of this, we have probed the scale-up of our alkoxy carbonylation chemistry. Our initial efforts were directed at performing the reaction in batch mode using a multimode microwave reactor equipped with eight heavy-walled quartz reaction vessels.¹¹ This gave us the capability to load up to eight reaction vessels and run them simultaneously by means of a reaction carousel. Using the ethoxycarbonylation of iodobenzene as a test reaction and starting with 0.1 mol of iodobenzene across the eight reaction vessels, we obtained an overall conversion of 91% and an isolated yield of 81% after chromatography. The disadvantage of this approach is that it takes time to load each vessel with reagents, pressurize each with carbon monoxide, and at the end of the reaction, decant each product mixture. Our next approach was to use a single reaction vessel of larger capacity. To achieve this we used a scientific microwave unit equipped with a 300-

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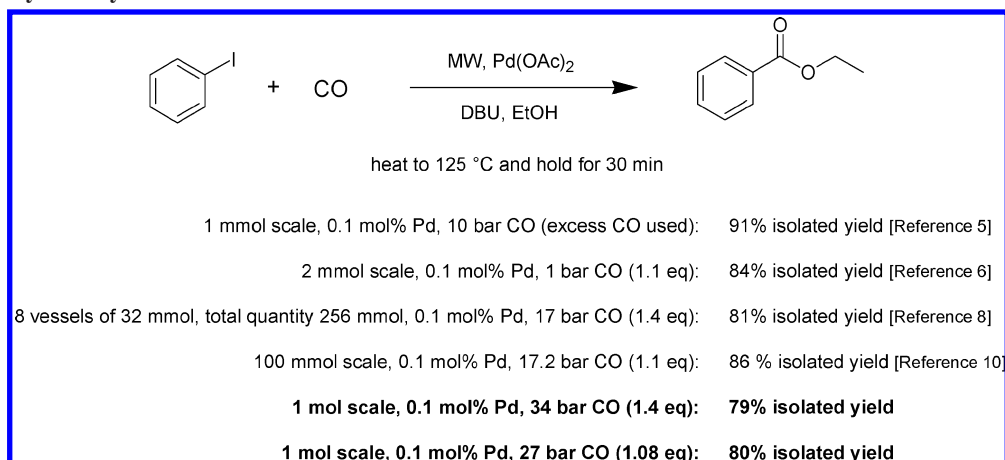
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Scheme 1. Alkoxy carbonylation of iodobenzene



mL Teflon vessel.¹² We performed the reaction on scales up to 75 mmol scale using the optimized conditions from our first small-scale protocol and obtained a quantitative conversion in the ethoxycarbonylation of iodobenzene. Turning to our near-stoichiometric methodology and deciding to perform the reaction on the 100 mmol scale, we calculated that an initial loading of 250 psi (17 bar) of CO would equate to 1.1 equivalents. Running the reaction on this scale and using a catalyst loading of 0.1 mol % resulted in >95% conversion to product and, after column chromatography, an 86% isolated yield. We were not able to scale up the reaction further since, at the 0.1 mol level, we were approaching the pressure limits of the apparatus. Knowing that further scaling of the reaction was going to be important, we have recently turned to a microwave unit comprising a single reaction vessel of 3.0 L capacity and a working volume of approximately 2 L. A discussion of the scale-up of our alkoxy carbonylation methodology to the 1 mol level as well as running multiple 50 mmol reactions simultaneously in the reactor is the subject of this technical note.

2. Results and Discussion

2.1. Microwave Apparatus Used. Our work was performed using the Milestone UltraCLAVE.^{10,13} The unit has found most application in the area of sample digestion.¹⁴ Its design is based on a high-pressure autoclave. It has a single, large reaction chamber of 3.0 L volume which is prepressurized with nitrogen to a level of approximately 15 bar. The prepressurization step also allows for easy introduction of reactive gases when required. Microwave energy is introduced into the reactor through a port located directly at the end of the waveguide. This design allows a microwave field of uniform intensity to be introduced directly into the reaction chamber overcoming the issues related to nonhomogeneous microwave field in large cavities. The pressurized chamber in the system serves simultaneously as the microwave cavity and the reaction vessel. By using this unit it is possible to run one large reaction of up to

2 L in volume in a Teflon vessel. In addition, it is possible to perform multiple smaller reactions at the same time in either Teflon, glass, or quartz vessels. This is achieved by placing all the loaded smaller reaction vessels into a dedicated rack. Uniform temperature conditions are achieved by positioning all the individual sample vessels in a pool of microwave-absorbing fluid. It is the effective temperature of this fluid that is monitored and controlled throughout the heating process. Since the entire microwave cavity is under pressure, in normal operation boiling never occurs in individual sample containers. Loose-fitting covers on each container prevent loss of sample or cross-contamination. We did not use these since we wanted to ensure a carbon monoxide environment was in each reaction vessel. The unit is able to operate at temperatures up to 260 °C and at pressures of 200 bar. All the reaction parameters (time, temperature, pressure, microwave power, stirring speed) can be monitored and controlled during the run through software installed on a dedicated touch-screen terminal. In using this unit, we envisaged simply using a mixture of nitrogen and carbon monoxide in the prepressurization stage, thus allowing us to perform our alkoxy carbonylation chemistry efficiently on a larger scale in one vessel or in a number of smaller vessels.

2.2. Scaling the Alkoxy carbonylation Reaction. To initiate our study we chose to focus on the ethoxycarbonylation of iodobenzene on the 1 mol scale. Our results are summarized in the context of our previous reports in Scheme 1. We decided first to perform the reaction on the 1 mol scale using 1.4 stoichiometric equivalents of carbon monoxide. We placed the 3.0 L capacity Teflon vessel containing the iodobenzene, DBU (1.1 equiv), palladium acetate (0.1 mol %), and ethanol (1.8 L) into the UltraCLAVE microwave unit. After first purging the reactor with nitrogen three times, we then loaded with nitrogen to a pressure of 8 bar before loading with 34 bar of CO (calculated to be 1.4 equiv) and then a further 15 bar of nitrogen for a total pressure of 57 bar. This sequence was important since the internal pressure forms the seal between the vessel and the lid of the unit. For safety reasons we wanted to ensure a tight seal before loading the carbon monoxide into the reactor and thus prepressurized to greater than the sealing limit with nitrogen first. We then heated the contents of the reactor to 125 °C over the period of 15 min and held at this temperature for 30 min. During the course of the reaction a drop in pressure to 40 bar

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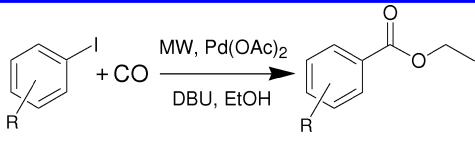

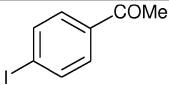
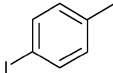
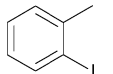
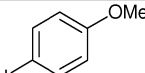
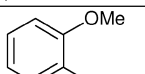
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was observed, this clearly indicating consumption of the carbon monoxide. Upon completion of the heating stage, we then allowed the reactor to cool to 55 °C before slowly releasing the residual pressure (32 bar) into a well-ventilated area. The cool-down phase was somewhat lengthy (approximately 45 min) because of the significant size of the vessel and the thick cavity walls. After removal of the reaction vessel from the unit and workup of the product mixture, pure ethyl benzoate was obtained in 79% yield, this being comparable to that obtained in our previous smaller-scale studies.

Our next objective was to perform the reaction using a near-stoichiometric loading of carbon monoxide. This methodology has significant advantages when working at larger scales, the major improvement being in safety. When working with a near-stoichiometric loading of carbon monoxide not only is the overall inventory of gas smaller, but also almost all the CO has been consumed at the end of the reaction, thus limiting the quantity liberated to the atmosphere upon depressurizing the reactor to access the vessel. By reducing the amount of CO used, it may also be possible to prolong the lifetime of catalysts and increase turnover numbers, and if using radiolabeled carbon monoxide, this methodology would represent a significant cost saving since isotopically labelled CO is expensive. Working on the 1 mol scale we attempted the ethoxycarbonylation of iodobenzene using a 1:1.08 stoichiometric ratio of aryl iodide to carbon monoxide. We calculated that this equated to an initial CO loading of 27 bar. Again, after purging with nitrogen three times, we first ensured effective sealing of the vessel in the unit by prepressurizing with nitrogen (11 bar) before loading the carbon monoxide followed by a further 12 bar of nitrogen, giving a total initial pressure of 50 bar. Using the same heating program as before, we held the reaction mixture at 125 °C for 30 min. Upon cooling the reaction vessel, venting residual pressure, and working up the product mixture, we obtained an 80% isolated yield of ethyl benzoate. This shows that the reaction can be performed using a near-stoichiometric loading of carbon monoxide on the 1 mol scale with a product yield comparable to that obtained in our initial 1 mmol trials in method optimization studies or to our efforts in scaling the reaction to the 0.1 mol level.

2.3. Performing Multiple Alkoxycarbonylation Reactions Simultaneously. In the knowledge that we could scale-up our alkoxycarbonylation reaction in one vessel, we next wanted to attempt a scale-up of six individual ethoxycarbonylation reactions simultaneously using the microwave unit, each being performed at the 50 mmol level. To achieve this we loaded six substrates into individual 150- mL capacity glass reaction vessels, choosing iodobenzene, 2-iodotoluene, 4-iodotoluene, 4-iodoanisole, 2-iodoanisole, and 4-iodoacetophenone. To each we added DBU (1.1 equiv), palladium acetate (0.1 mol %), and ethanol (90 mL). The loaded vessels were placed (without covers) into a rack, and this in turn was attached to the lid of the microwave unit. A volume of ethanol was placed inside the large Teflon vessel, thus serving as the requisite pool of microwave-absorbing fluid. After making sure that the smaller vessels sat in the pool of ethanol in the larger vessel and ensuring effective sealing in the unit by prepressurizing with nitrogen, we loaded the reactor with 1.08 stoichiometric

Table 1. Alkoxycarbonylation of aryl iodides on the 50 mmol scale^a

		
Entry	Aryl halide	Conversion (%)
1		>99
2		>99
3		99
4		97
5		94
6		91

^a 50 mmol aryl halide, 90 mL of ethanol, 0.1 mol % Pd(OAc)₂, 1.1 equiv of DBU, 8 bar CO (1.08 equiv). Reaction mixture ramped from rt to 125 °C over the period of 15 min and held at this temperature for 30 min.

equivalents of carbon monoxide (8 bar, based on six 50 mmol reactions) followed by further nitrogen, to give a total initial pressure of 50 bar. Using the same heating program as before, we held the reaction mixture at 125 °C for 30 min. After cooling the reaction vessel and venting residual pressure, the six vessels were removed from the microwave unit and products isolated. The results are shown in Table 1. In each case an excellent conversion to the desired ester product was observed. Of note is that no observed cross contamination of the reaction mixtures was observed. This confirms that, under the conditions used, the prepressurization of the microwave cavity ensures that the partial pressures of the aryl iodide starting materials or ester products never exceed that required to allow them to exit the individual vessels. The use of a moderating fluid allows us to negate problems arising from differential microwave absorptivity of reaction mixtures when performing parallel syntheses. Previous results from our group have shown that the heating characteristics of the substrate can affect significantly the outcome of a reaction, particularly in cases when reactions involving poorly microwave-absorbing solvents are used.¹⁵ Another parameter for consideration when performing a synthesis using a range of substrates in a multimode microwave apparatus is into which vessel the temperature probe should be placed and thus is used as the control. In our case this is not an issue since the temperature probe is inserted into the moderating fluid.

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3. Summary

In this technical note we have shown that alkoxycarbonylation reactions can be scaled up successfully in batch mode using a sealed-vessel multimode microwave unit. The ethoxycarbonylation of iodobenzene was performed on the 1 mol scale using both an excess and a near-stoichiometric loading of carbon monoxide. Yields comparable to those previously reported for the reaction on smaller scales were obtained. Six different alkoxycarbonylation reactions were performed simultaneously on the 50 mmol scale using a near stoichiometric loading of carbon monoxide with excellent conversions in each case.

4. Experimental Section

4.1. General Experimental. All reagents were obtained from commercial suppliers and used without further purification. ^1H NMR spectra were recorded at 293 K on a 300 or 400 MHz spectrometer.

4.2. Equipment. Reactions were performed in a Milestone UltraCLAVE multimode microwave unit. The instrument consists of a continuous microwave power delivery system with power output from 0–1000 W. Operating pressures up to 200 bar and temperatures up to 260 °C can be achieved. Single reactions were performed in a 3.0-L capacity Teflon vessel. The temperature of the contents of the vessel was monitored using a shielded thermocouple inserted directly into the reaction mixture by means of a Teflon coated stainless steel thermowell. The contents of the vessel 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. To perform multiple reactions at the same time, 150-mL capacity Teflon reaction vessels were used. Ethanol was employed as the moderating fluid, and the temperature of this was recorded during the course of a run. In all cases, the microwave cavity was prepressurized to 50 bar. Pressure was measured using a transducer. Product mixtures were cooled at the end of a run by passing a flow of coolant around the outside of the stainless steel microwave cavity. All operations (sealing, pressurizing, heating, cooling, venting, and opening the vessel in the microwave cavity) were undertaken using computer control. During the course of a run, integrated sensors continuously monitored and displayed internal pressure, temperature, and microwave power applied. The software dynamically adjusted the applied microwave power in real time to follow a predefined temperature profile.

4.3. Experimental Procedures for the Reactions Performed in This Study. *Ethoxycarbonylation of Iodobenzene Using an Excess of Carbon Monoxide.* Palladium acetate (220 mg, 1 mmol) and ethanol (1.8 L) were combined in a 3.0 L Teflon vessel placed into the microwave unit and stirred. DBU (167.0 g, 163.9 mL, 1.1 mol) and iodobenzene (204.0 g, 112.1 mL, 1 mol) were added. The microwave cavity was closed and the vessel loaded and purged three times with nitrogen. In cycle 1, the vessel was pressurized with nitrogen from atmospheric to 30 bar, and then the pressure was released to 8 bar. In cycles 2 and 3 the pressure was raised to 30 bar and then released back to 8 bar. Following this, the vessel was loaded with 34

bar of carbon monoxide (1.4 equiv based on iodobenzene) followed by 15 bar of nitrogen, this giving a total pressure of 57 bar. The reaction mixture was heated to 125 °C over the period of 15 min. The contents of the vessel were then held at this temperature for 30 min. The reaction mixture was stirred throughout the run. Upon completion of the heating stage, the reaction mixture was cooled to 55 °C, this taking 45 min; then the reaction chamber was slowly vented and opened. The contents of the reaction vessel were added into diethyl ether (500 mL). The brown precipitate that formed (DBU·HCl salt) was filtered off, dissolved in water, and extracted with diethyl ether (3×50 mL). All the organic phases were collected, concentrated under reduced pressure, and washed with 1 N HCl (2×150 mL) and saturated KCl solution (3×150 mL). After adding petroleum ether (200 mL of bp 30–40 °C), the organic phase was washed further with distilled water (2×50 mL) and dried over MgSO_4 . It was then concentrated under reduced pressure to afford ethyl benzoate (119 g, 79% yield).

Ethoxycarbonylation of Iodobenzene Using a Near-Stoichiometric Loading of Carbon Monoxide. An identical procedure was used with the exception that in the final stage of the nitrogen purge cycle the vessel was pressurized with nitrogen from atmospheric to 30 bar, and then the pressure was released to 11 bar. Following this, the vessel was loaded with 27 bar of carbon monoxide (1.08 equiv based on iodobenzene) followed by 12 bar of nitrogen, this giving a total pressure of 50 bar. Upon workup ethyl benzoate (120 g, 80% yield) was obtained.

Ethoxycarbonylation of Six Aryl Iodides Using a Near-Stoichiometric Loading of Carbon Monoxide. To each of six Teflon vessels (150 mL capacity) equipped with a magnetic stir bar and placed into a six-position rack were added palladium acetate (11 mg, 0.05 mmol) in ethanol (90 mL), DBU (8.37 g, 8.2 mL, 55 mmol), and aryl iodide (50 mmol). Ethanol (400 mL) was placed into the 3.0 L Teflon vessel as a moderating fluid. The vessel was loaded and purged three times with nitrogen. In cycle 1, the vessel was pressurized with nitrogen from atmospheric to 30 bar, and then the pressure was released to 8 bar. In cycles 2 and 3 the pressure was raised to 35 bar and then released back to 11 bar. Following this, the vessel was loaded with 8 bar of carbon monoxide (1.08 equiv based on six 50 mmol reactions) followed by 31 bar of nitrogen, this giving a total pressure of 50 bar. An identical heating program was used as in the previous experiments (heat to 125 °C over 15 min and hold for 30 min). After cooling and venting, each product mixture was worked up individually using the same protocol as before but scaling down volumes of solvents and water by a factor of 20.

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