

A Continuous-Flow Approach to Palladium-Catalyzed Alkoxy carbonylation Reactions

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ABSTRACT: Using a continuous-flow approach, it is possible to perform alkoxy carbonylation reactions of aryl iodides. Optimized reactor design allows for adequate mixing of gaseous and liquid reagents. Reactions are performed at rates of around 3 mL/min and at concentrations of 1 M, allowing for significant volumes to be processed per unit time. Palladium acetate (0.5 mol %) is used as the catalyst without the need for an additional ligand.

INTRODUCTION

Palladium-mediated carbonylation chemistry is an important tool in the synthetic chemist's portfolio.^{1,2} Using aryl halides as starting materials, carboxylic acids and esters can be prepared by using water or alcohols as nucleophiles, respectively. In our laboratory we have developed methodologies for performing these transformations within 30 min using microwave heating.^{3,4} The chemistry can be scaled up quite effectively in sealed batch mode.^{5,6} However, two issues that arise are that, first, a significant quantity of toxic carbon monoxide has to be loaded into the reaction vessel and, second, under some conditions, the palladium catalyst can be deactivated over time by carbon monoxide. To overcome these drawbacks, we developed a methodology that only requires a near stoichiometric quantity of carbon monoxide.⁷ Recently, we have turned our attention to a continuous-flow approach using a dual-phase gas–liquid flow to effect alkoxy carbonylation of aryl iodides using conventional heating as an alternative to batch microwave heating.

The development of flow approaches to synthetic organic transformations is a topic of considerable interest in current literature.^{8,9} The use of reactive gases as reagents has received attention. Hydrogenation reactions can be performed using the now ubiquitous H-cube system.^{10,11} Gases such as oxygen,¹² fluorine,¹³ and dimethylsulfide¹⁴ have also been used in flow. The use of carbon monoxide in flow chemistry is not unprecedented. Aminocarbonylation reactions have received particular attention¹⁵ as has the radical carbonylation of alkyl halides.¹⁶ However, a theme running through much of the literature reporting the application of gases in flow mode is the use of microscale equipment. Our interest lay in performing chemistry on the mesoscale, allowing us to process larger quantities of material per unit time. We therefore embarked on a study with the objective of developing an approach for alkoxy carbonylation in flow mode. This required designing apparatus, optimizing reaction conditions, and substrate screening. Our results are presented here.

RESULTS AND DISCUSSION

Our first objective was to modify our commercially available flow reactor so that we could reliably and reproducibly introduce an input of gas. In order to ensure effective reaction, the contact

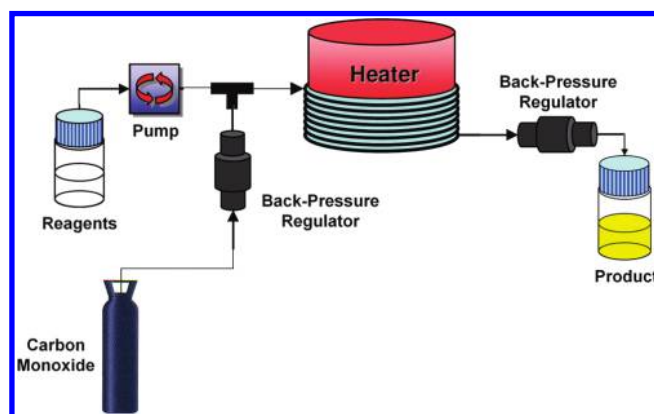


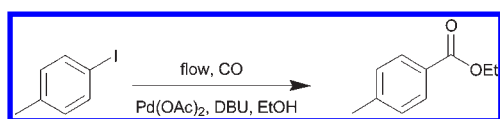
Figure 1. Optimized setup for reactions involving reactive gases as reagents.

area between the gas/liquid interface was an important factor to consider. Our optimized experimental setup is shown in Figure 1. We introduced the gas through a back-pressure regulator and at an angle of 90° to the liquid flow. The gas/liquid flow then entered the heated zone. By using a PTFE coil mounted on an aluminium mandrel, we were able to observe the bubbles, noting the size and spacing between them as they passed through the reactor coil. Our desired bubble size was between 0.5 and 1.0 mm in cross section, the bubbles being separated by slugs of reaction mixture of between 1.0 and 2.0 mm.

Our next step was to find suitable conditions for the alkoxy carbonylation reaction, the results being shown in Table 1. As a starting point we turned to the conditions developed for our batch approach using microwave heating, namely using palladium acetate as catalyst, DBU (1,8-diazobicyclo[5.4.0]undec-7-ene) as base and performing the reaction in the requisite alcohol as solvent at 120 °C for 20 min. Using 4-iodotoluene (1 mmol) as our aryl halide starting material, ethanol as the nucleophile and solvent (10 mL), DBU (1.1 equiv) as base and 1 mol % Pd(OAc)₂ as catalyst we passed the reagents through the unit

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Table 1. Optimization of conditions for the alkoxycarbonylation reaction

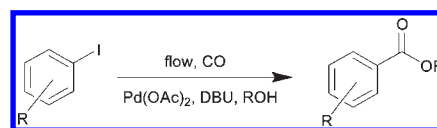
entry	reaction conditions ^{a,b}	conv (%) ^c
1	1 mmol, 1 mol % Pd, 10 mL EtOH, 0.3 mL/min	50
2	1 mmol, 1 mol % Pd, 10 mL EtOH, 0.4 mL/min	68
3	1 mmol, 1 mol % Pd, 10 mL EtOH, 1 mL/min	56
4	1 mmol, 1 mol % Pd, 20 mL EtOH, 0.6 mL/min	20
5	1 mmol, 1 mol % Pd, 2 mL EtOH, 1.2 mL/min	75
6	1 mmol, 1 mol % Pd, 2 mL EtOH, 1.2 mL/min	88 ^d , 94 ^e
7	10 mmol, 0.5 mol % Pd, 10 mL EtOH, 1.2 mL/min	91
8	10 mmol, 0.1 mol % Pd, 10 mL EtOH, 1.2 mL/min	15
9	10 mmol, 0.1 mol % Pd, 5 mL EtOH, 1.2 mL/min	75

^a Reactions were performed at 120 °C using a CO pressure of ~180 psi and 1.1 equiv of DBU. ^b For clarity, changes in reaction conditions from entry 1 are noted in bold. ^c Determined using ¹H NMR spectroscopy. ^d After two passes through the heated zone. ^e After three passes through the heated zone.

at 0.3 mL/min. Accounting for the added effect of the gas flow, this gave a residence time in the heated zone of approximately 20 min. We obtained a 50% conversion to the desired ethyl ester product (Table 1, entry 1).

Increasing the flow rate to 0.4 mL/min had a beneficial effect on the outcome, the conversion rising to 68% (Table 1, entry 2). However, at flow rates greater than this, the conversion dropped (Table 1, entry 3). Reducing the concentration of the reaction mixture had a deleterious effect (Table 1, entry 4) but increasing the concentration 5-fold while also increasing the flow rate improved the product conversion significantly (75%; Table 1, entry 5). We took the product mixture from this run and resubmitted it to the reaction conditions (with no additional catalyst or base). After a second pass the conversion reached 88% and, after a third pass, 94% (Table 1, entry 6). We did try using a slower rate and a single pass, but in order to maintain steady bubble flow, we found that there was a threshold rate that we could not go below. Therefore, multiple passes through the reactor proved to be a more reliable approach.

While leading to a high product conversion, passing the reaction mixture through the heated zone three times is laborious. We decided to scale up the reaction and determine whether a one-pass strategy was feasible. Working on a significantly larger scale (10 mmol) and at a higher concentration (1 M) and reducing the catalyst loading to 0.5 mol % we were pleased to find that a 91% conversion to product could be obtained after only one pass through the heated zone. During a few of the runs, small quantities of palladium black appeared as tiny particles in the reactor coil. This particulate matter did not interfere with the flow under these conditions, nor did it lead to any immediate clogging of the back-pressure regulator at the exit of the heated zone. At higher concentrations or catalyst loadings we saw the formation of larger quantities of palladium black, and blockage of the back-pressure regulator ultimately occurred. As a result, product conversions were compromised (Table 1, entries 8 and 9, respectively). Thus, our optimal conditions were 1 M

Table 2. Alkoxycarbonylation of aryl halides^a

entry	aryl halide	alcohol	conversion (%) ^b
1		EtOH	91 (86) ^c
2		EtOH	85
3		EtOH	88 (81) ^c
4		EtOH	71, 94 ^d
5		EtOH	46
6		EtOH	42, 84 ^d
7		EtOH	31, 72 ^d
8		EtOH	55, 91 ^d
9		EtOH	88
10		<i>n</i> -PrOH	88
11		<i>i</i> -PrOH	58, 85 ^d

^a Reactions were performed on the 10 mmol scale at 1 M concentration, 0.5 mol % Pd(OAc)₂ as catalyst, 1.1 equiv of DBU as base, a gas flow at ~180 psi, and a reagent flow rate of 1.2 mL/min, corresponding to a total flow rate of 3.3 mL/min and a residence time in the heated zone (120 °C) of approximately 4 min. ^b Determined using ¹H NMR spectroscopy ^c Isolated yield. ^d Data for the first and a second pass through the heated zone.

concentration, 0.5 mol % Pd(OAc)₂ as catalyst, 1.1 equiv of DBU as base, a gas flow at ~180 psi, and a reagent flow rate of 1.2 mL/min, corresponding to a total flow rate of 3.3 mL/min and a residence time in the heated zone (120 °C) of approximately 4 min.

With the optimized conditions in hand, we screened a range of aryl iodides to probe the substrate scope of the methodology. The results are shown in Table 2. A range of aryl iodides can be converted to the ethyl esters including ortho-substituted examples (Table 2, entries 6 and 7). A representative heteroaromatic substrate, 3-iodopyridine, gave a good yield of the desired ester (Table 2, entry 9). Both 1-propanol and 2-propanol can be used as the alcohol for the reaction (Table 2, entries 10 and 11). With some less reactive substrates, a second pass through the heated zone was required in order to obtain higher, more acceptable product conversions (Table 2, entries 6, 7, 8, and 11). In the case

of 4-iodoacetophenone, solubility issues meant that the reaction had to be performed at a concentration of 0.5 M, and this resulted in only a moderate conversion to the ester product (Table 2, entry 5). Overall, product conversions are on par with those obtained using the analogous batch approach.

SUMMARY

In summary, using a continuous-flow approach, it is possible to perform alkoxy-carbonylation reactions of aryl iodides. Reactions were performed using 0.5 mol % palladium acetate as catalyst with no additional ligand required. The methodology offers an alternative to previous approaches in batch mode using microwave heating.

EXPERIMENTAL SECTION

General Experimental. For the alcohol substrates, 200 proof (anhydrous) ethanol was used, and commercially available anhydrous 1-propanol and 2-propanol were used. Reactions were run without the need for exclusion of air. CAUTION: Working with CO gas under pressurized conditions is not without risk in case of a failure in the PTFE coil during the course of a reaction. Performing the chemistry in a fume cupboard is essential, and locating a carbon monoxide detector outside the fume cupboard but in close proximity to the flow unit is advisable.

Apparatus. Experiments were performed on a Uniqsis FlowSyn system, modified in-house for use with gaseous reagents. A carbon monoxide tank was fitted with a regulator capable of delivering pressures of up to 250 psi. This was interfaced with a length of 1 mm id, 3 mm od PTFE tubing, this being attached to one of the ports of the built-in T-piece on the FlowSyn system linked to the pressure transducer and pumps. This enabled us to monitor CO pressure directly using the FlowSyn. A second port (opposite that used for inputting gas) was blocked using a plug. To the remaining empty port was attached a length of 1 mm id, 1.57 mm od PTFE tubing, and this in turn attached to a second T-piece via a back-pressure regulator (40 psi) as a bridge. The output from one of the two FlowSyn pumps was connected to the second T-piece at an angle of 90° (The pump is designed to push material one way only, this preventing material going back through the pump head.). The 14 mL PTFE coil was attached to the third port and the third T-piece. Unlike normal use when reagents are passed in at the bottom of the coil and exit at the top, in this case the coil was inverted such that the reaction stream entered the top of the coil and exited at the bottom. We found this led to more consistent flow of bubbles of the desired size. After exiting the heated zone, material was passed through a second back-pressure regulator (100 psi). The liquid output from this was collected in Erlenmeyer flasks.

General Procedure. The ethoxy-carbonylation of 4-iodotoluene. A solution of anhydrous ethanol (10 mL) and DBU (1.64 mL, 11 mmol, 1.1 equiv) was thoroughly mixed before adding Pd(OAc)₂ (12.4 mg, 0.05 mmol). The solution was again mixed thoroughly. If particulate matter remained, the mixture was sonicated in an ultrasound cleaning bath to facilitate dissolution.

With this solution prepared, the Uniqsis Flowsyn reactor was next readied. After flushing the system with anhydrous ethanol for at least 2 min at 7.0 mL min⁻¹ or greater, the aluminium block was heated to 120 °C. The flow rate was reduced to 1.2 mL

min⁻¹, and the CO gas line was opened with an approximate 170 psi pressure. The pressure was then varied slightly until a steady bubble size and consistent flow rate were achieved (typically, between 160 and 196 psi). Flow rates did vary slightly but averaged around 3.3 mL min⁻¹ once optimal bubble size had been achieved.

Once preparation of the reactor was complete, 4-iodotoluene (2.1835 g, 10 mmol) was added, and the reagent line was placed inside the prepared solution, reaching the bottom of the tube. The line was secured to the test tube and the reactor pump switched from “solvent” to “reagent”. Collection began immediately after this switch to ensure all product was collected. After the reaction mixture had been completely charged into the reactor, the reactor pump was turned back to “solvent”. Collection for an additional 12 min was undertaken to ensure that all reagents had left the reactor.

To the product mixture was added diethyl ether (50 mL) followed by ~80 mL of brine, and the biphasic mixture was well mixed. The layers were separated, and the aqueous layer was re-extracted with diethyl ether (3 × ~80 mL each). The combined organic layers were then mixed with an equal volume (~300 mL) of hexanes. This facilitated removal of ethanol from the diethyl ether layer. After about a 10-min wait, the ethanol layer was removed. The diethyl ether layer was then dried with MgSO₄ and filtered. The solvent was removed by rotary evaporation and the product conversion determined by ¹H NMR spectroscopy.

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