

RAPID GAS-LIQUID PALLADIUM CARBOXYLATIVE CROSS-COUPLING REACTIONS USING A GLASS FABRICATED MICROFLUIDIC CHIP FOR APPLICATIONS IN ^{11}C -RADIOLABELLING

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Abstract

A series of gas-liquid palladium catalysed carbonylative cross-coupling reactions, forming secondary amides, were carried out using a glass fabricated microfluidic device. Improved yields from the microreactions were obtained in short reaction times (< 2 min) and were higher in all cases when compared to their corresponding batch reactions. We are currently in the process of applying our reaction set-up to [^{11}C]CO radiolabelling to be used in PET (Positron Emission Tomography) imaging.

Keywords: Carbonylation, cross-coupling, palladium, gas-liquid reaction, medical imaging, Positron Emission Tomography

1. Introduction

PET (Positron Emission Tomography) imaging is a rapidly emerging field in medical imaging. The synthesis of ^{11}C isotopically labelled compounds for use in PET scans is a particularly challenging area of chemistry.¹ These challenges arise from the short half-lives associated with positron emitters (^{11}C $t_{1/2}$ = 20.4 min) and from the difficulties of working with radioactive compounds. Carbonylative cross-coupling reactions²⁻⁴ (Fig. 1) are becoming an increasingly important class of reaction in the synthesis of ^{11}C -labelled compounds⁵ owing to their convenient one step transitions to a number of biologically interesting functional groups.

Carbonylation reactions are conventionally carried out at elevated pressures of carbon monoxide in the presence of a palladium-phosphine catalyst and can take

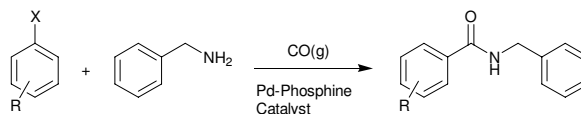


Figure 1. Synthesis of *N*-benzylbenzamide via the palladium catalysed carbonylative cross-coupling reaction.

many hours to go to completion. The rates of these reactions are dependent on a number of factors such as the aryl halide species, the nature of the catalyst, the nucleophilic species, the pressure and the temperature of the system. The insertion step of the carbonylative catalytic cycle can be rate limiting owing to the poor transport of carbon monoxide into the solution phase. This step of the catalytic cycle can be enhanced by

increasing pressure in the system or by improving contact between gas and liquid phases; microreactor devices provide a potentially very useful way of doing this.^{6,7} Here we report a series of carbonylation reactions using a glass fabricated microfluidic chip with the aim of applying it to [¹¹C]CO radiolabelling reactions.

2. Experimental

The microfluidic device (figure 2a) was constructed from a glass substrate using chemical wet etching techniques. The liquid and gaseous reagents were introduced *via* separate entrance ports and mixed on chip using a mixing-tee configuration. Our reaction set-up (figure 2b) involved injecting a mixture of arylhalide, palladium-phosphine catalyst and benzylamine into the chip and mixing with a constant flow of CO gas heated; the device was heated to 150 °C. Liquid flow rates of 10 µl/min and gas flow rates of 2 sccm were used for these experiments which impose an annular type flow regime on the system generating high gas-liquid interfacial contact areas.

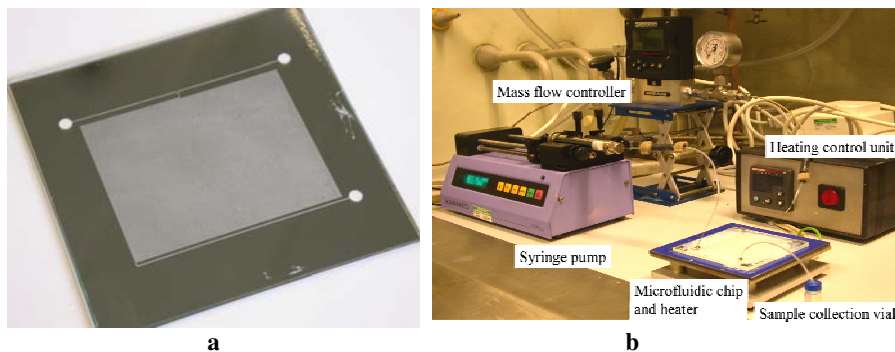



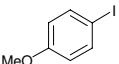

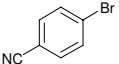
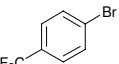
Figure 2. (a) A photograph of the microfluidic chip used in the carbonylation reactions. The channel is 5 metres long, 200 µm wide and 75 µm deep (volume = 75 µl). (b) Reaction set-up for the carbonylative cross coupling reaction using a microfluidic chip.

3. Results and Discussion

A series of different arylhalide substrates (table 1) with varying electronic properties were investigated for the carbonylative cross-coupling reaction with benzylamine and carbon monoxide using Pd(dppp)Cl₂ catalyst. The highest yield was obtained for entry 1 owing to the facile nature of the oxidative addition step of iodoaryl groups to palladium(0). In contrast entry 2, also an iodoaryl, gave lower yields (55%) due to the electron donating *para* methoxyl group slowing down the oxidative addition step. The bromoaryl substrates entries 3-5 gave high yields of amides owing to their electron withdrawing groups enhancing the oxidative addition step.

The insertion of CO into the catalytic cycle forming the acyl palladium(II) complex can be rate limiting owing to the poor transport of carbon monoxide into the solution phase. The increase in yields obtained by the microreactions can be attributed to the enhanced heat transfer and enhanced transport of CO gas into the liquid phase as a direct result of the increased interfacial gas-liquid contact area generated within our microfluidic device.

Table 1

Entry	Substrate	Yield (%) ^[1]
1		87
2		55
3		75
4		83
5		85

4. Conclusions

In conclusion a microstructured device has been used to perform gas-liquid carbonylation reactions to good effect. High yields of amide products were obtained in very short residence times (<2 min) for these conventionally slow reactions. Compared to traditional batch scale reactions, the gains in yields over this time period obtained demonstrate a distinct advantage in using microdevices for these gas-liquid phase reactions. We are currently in the process of adapting our reaction set-up to radiolabelling experiments using ¹¹C for the synthesis of ¹¹C labelled amide and ester molecules.

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¹ Average of three runs based on the arylhalide and calculated by GC using diphenyl ether as internal standard.