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Design of a capillary-microreactor for efficient Suzuki coupling reactions

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Abstract—A Pyrex glass capillary (0.4 mm internal diameter) microreactor was developed and used for Suzuki coupling reactions. Capillary-microreactors are more attractive than photolithographic microfluidic devices in terms of simplicity, low cost and ease of handling. Compared with the conventional synthesis procedure, our approach of using a capillary-microreactor offers a convenient and highly efficient means to optimize reaction conditions and the performance of catalysts. The procedure exhibits good precision, reproducibility and high reaction yield for a range of reactants investigated.

1. Introduction

Microfluidic technology offers many benefits in various fields including chemistry, biology and medicine.[1] Over the past decade, the trend towards miniaturization has been driven by the need for rapid, simple and on-line measurements in chemical synthesis, pharmaceutical screening, medical diagnostics and environmental analysis.[2–6] A few reports have demonstrated the fundamental advantages of miniaturized systems, as compared to conventional large-scale synthesis.[7–11] Owing to their large surface area, microfluidic devices have excellent mass and heat transfer properties. Microreactors represent a promising way to reduce time and costs of chemical processes with increased selectivity and safety for chemical synthesis and biochemical reactions.[12,13] In synthesis, a large number of applications have demonstrated the fundamental advantages of miniaturized systems such as lab-on-a-chip devices compared with a conventional, large-scale set-up.[14]

Photolithographic microfabrication is a useful methodology for the fabrication of miniaturized devices. However, design and fabrication of even simple fluidic systems require clean room facilities and expensive instrumentation. To overcome these problems, we describe here a simple, inexpensive and disposable capillary-microreactor in combination with HPLC analysis. Recently, capillary-microreactors have been utilized in various fields including peptide analysis and oxidation reactions.[15,16] However, the present study discusses the Suzuki coupling reaction[17,18] in a capillary-microreactor involving a single reactant, or a mixture of reactants.

In our approach, the reaction device is a glass capillary (0.4 mm internal diameter) connected to a power supply (Fig. 1). Within the capillary, the palladium nanoparticles interact with the reactants under an applied potential and enhance the efficiency of the

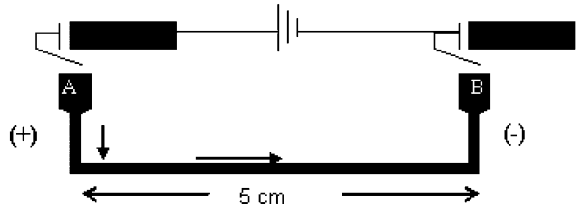

Figure 1. Schematic diagram of the capillary-microreactor.

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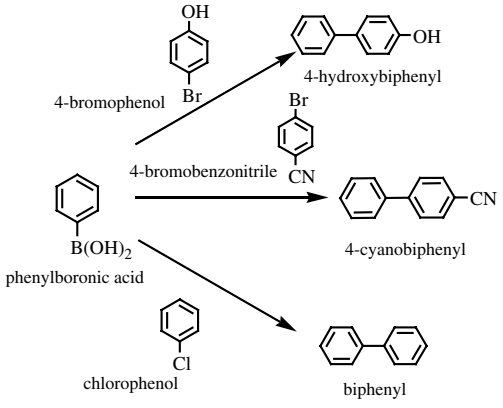
coupling reaction. Compared with conventional synthesis, a higher yield is expected under optimized reaction conditions.

2. Synthesis of palladium nanoparticles

The palladium nanoparticles were prepared from palladium acetate.[19–21] Briefly, 50 mg of palladium acetate was added to a solution of poly(*N*-vinyl-2-pyrrolidone) (2.5 g) in 150 mL methanol and the mixture was refluxed for 2 h. The resulting brown colloidal solution was filtered using a 0.2-μm Teflon filter and concentrated to 25 mL. A drop of the colloidal solution was spotted onto Formvar stabilized copper grids, and a JEOL (Tokyo, Japan) TEM system was used to characterize the size of the nanoparticles.

3. Suzuki coupling reaction by conventional method

The Suzuki coupling reactions between phenylboronic acid and halobenzenes were carried out using palladium nanoparticles, as described previously.[22] For conventional route Suzuki coupling, sodium acetate (0.49 g, 6 mmol), phenylboronic acid (0.37 g, 3 mmol) and a mixture (0.20 g, 1 mmol) of each reactant (i.e., chlorobenzene, 4-bromobenzonitrile and 4-bromophenol) was added to 150 mL of a 3:1 mixture of acetonitrile:water (see the reaction, Scheme 1). The solution was heated to 80 °C, followed by the addition of 5 mL of the palladium nanoparticle solution to start the reaction. The reaction mixture was refluxed for a total of 12 h and the reaction yields were quantified by HPLC (Table 1).



Scheme 1. Coupling reactions tested with the microreactor.

4. Suzuki coupling reaction in a capillary-microreactor

The basic arrangement of the capillary-microreactor is depicted in Figure 1. Polypropylene pipette tips were inserted at the end of the capillary tube to serve as reservoirs. The capillary (5 cm length) and reservoirs A and B were filled with 50 mmol of phosphate buffer solution (pH 12) mixed with 5% of palladium catalyst. Extreme care was taken to ensure that air bubbles were absent inside the capillary tube (by measuring a constant current). For reactions, a 5 μL of reactant mixture (i.e., 3 mmol of phenylboronic acid, 4.8 mg in 10 mL); 1 mmol of 4-bromophenol (1.7 mg in 10 mL); 1 mmol of chlorobenzene (1.1 mg in 10 mL) and 1 mmol of 4-bromobenzonitrile (1.8 mg in 10 mL) were introduced in the reservoir. A stoichiometry of 1:1 between the boronic acid and the halo compound was maintained. For individual reactions, 5 μL of reaction mixture containing 1 mmol of phenylboronic acid with 1 mmol 4-bromophenol or 4-bromobenzonitrile or chlorobenzene was introduced. A reaction potential of 5 kV and 100 μA current were applied to reservoir A, and reservoir B was connected to ground. Platinum wires were used as electrodes. The direction of the applied potential was switched alternately (i.e., initially A+ve and B−ve, then A−ve and B+ve and so on) after every 5 min at constant current and the reaction was monitored for 40 min at room temperature. The reaction yields were quantified by HPLC.

5. Optimization of Suzuki coupling reaction in the capillary-microreactor

In order to optimize the Suzuki coupling reactions in the capillary-microreactor, analytical factors such as sample pH, length of the capillary, applied potential and reaction time were studied. Temperature was kept constant at room temperature throughout the reactions. Initially, individual reactions (Scheme 1) were carried out separately. The results were then compared with those involving a mixture of all three halo compounds and the boronic acid. However a 1:1 stoichiometry between the boronic acid and halo compound was maintained in both routes. To our surprise, no significant difference in the yield was observed. Therefore, the conditions of the respective coupling reactions were optimized based on a mixture of reactants.

Quantitative yields were determined by separate calibration curves. The analytical factors were evaluated in

Table 1. Comparison of reaction efficiency in capillary-microreactor with conventional synthesis via Scheme 1

Reactants	Products	Yield % in conventional procedure[b]	Yield % in capillary-microreactor	
			Individual reactions[a]	Mix reactions[a]
Phenylboronic acid and 4-bromophenol	4-Hydroxybiphenyl	17	78	82
Phenylboronic acid and 4-bromobenzonitrile	4-Cyanobiphenyl	23	89	88
Phenylboronic acid and chlorobenzene	Biphenyl	11	83	95

[a] Reaction was performed in a 5 cm capillary-microreactor for 40 min at 5 kV applied potential, 100 μA current, rt and pH 12, individual reaction involves only one bromo compound whereas the mix reactions involve all three bromo compounds.
[b] The boronic acid was reacted with a mixture of bromo compounds in a stoichiometry of 3:1:1:1.

triplicate. There was an increase in the size of the catalyst particles after 30 min reaction, causing coagulation in the microreactor. This is attributed to Ostwald ripening, which has been reported previously for such particles.[20] However, we did not attempt to measure the palladium nanoparticle size distribution in this study. Due to the precipitation of the catalyst, the particles could be easily removed by filtration before HPLC analysis.

6. Reaction time

Reaction time is one of the most important parameters in the Suzuki coupling reactions. It was varied between 10 and 60 min and the reaction yield with respect to times shown in Figure 2. In general, the reaction yield increases with increase in reaction time, up to 40 min, which appears to be an optimum period.

7. Applied potential

In the capillary microreactor, the analytes mobility has been driven by electro osmatic flow and the flow could be controlled by the applied potential. Additionally, the higher applied potential increases the analyte interaction with the nanoparticles and enhances the reaction yield. The necessary applied potential to achieve a high yield was obtained by applying various applied potentials in the range of 1–5 kV at a constant current of 100 μA. Figure 3 shows the influence of the applied potential on the yield. As can be seen, a maximum product yield was obtained by using 5 kV.

8. Reaction pH

The influence of pH ranging from 2 to 12 on the yield of the coupling reaction in the capillary-microreactor was investigated. Figure 4 shows the liquid chromatogram of the product mixture after each reaction involving different starting materials (Scheme 1) for 40 min at a pH 8. The results are summarized in Figure 5.

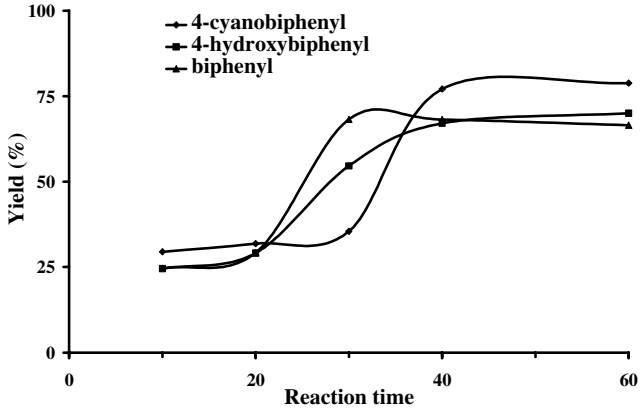


Figure 2. Effect of different reaction times on the product yield in the capillary-microreactor (at pH 12 and applied potential 3 kV, rt).

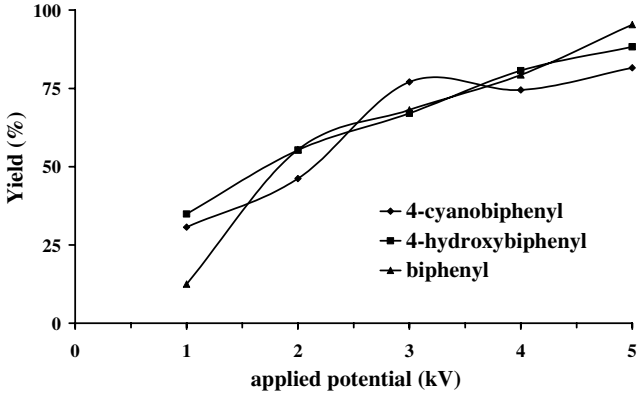


Figure 3. Effect of different applied potentials on the product yield in the capillary-microreactor (at pH 12 and reaction time 40 min, rt).

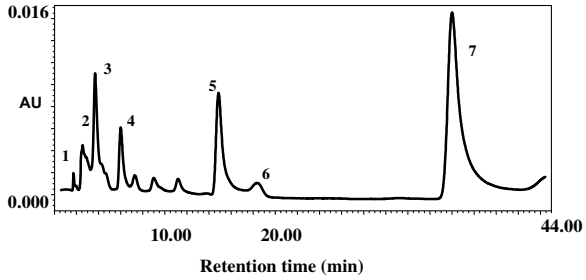


Figure 4. Liquid chromatogram of product mixture after Suzuki coupling reactions in the capillary-microreactor at pH 8. Peaks were identified as 4-bromophenol **1**, 4-bromobenzonitrile **2**, phenylboronic acid **3**, 4-hydroxybiphenyl **4**, 4-cyanobiphenyl **5**, chlorobenzene **6** and biphenyl **7** using standard samples.

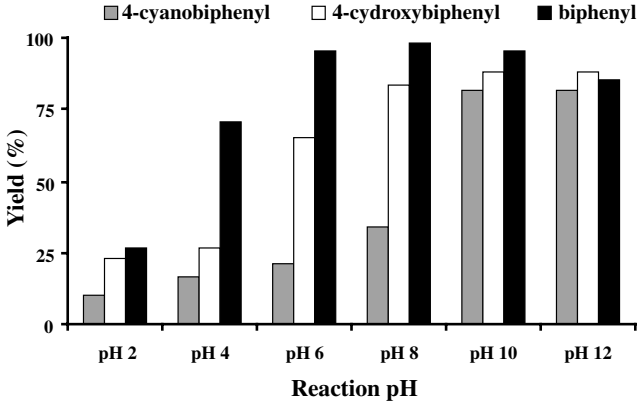


Figure 5. Effect of reaction pH on the product yield in the capillary-microreactor (at 40 min reaction time and applied potential 5 kV).

9. Length of the capillary-microreactor

An interesting problem in microdevices is the scaling factor that results when miniaturizing the volume of microreactors. It has been shown that for microdevices using an electrophoretic separation at constant field, resolution is proportional to the square of the channel length.[23] However, in our study no significant improvement in the reaction yield was obtained when the length of the capillary was increased from 3 to 7 cm.

10. Quantitative determination of Suzuki coupling reaction

To evaluate the reaction yield, the optimum reaction conditions (reaction time of 40 min, pH 12 and applied potential of 5 kV) were used with a 5 cm long capillary-microreactor. Representative results are summarized in Table 1. Compared with conventional synthesis, the capillary-microreactor provided higher reaction yields.

11. Mechanism of the reaction

The oxidative addition of bromoarenes to the surface of the Pd^0 nanoparticle is believed to be the first step in the coupling reactions.[24] Rate of the reaction can be enhanced by the incorporation of electron withdrawing groups on haloarenes[25] or electron rich ligands on palladium.[26] In our reactor, we believe that the applied potential increase the electron density on the surface of the palladium nanoparticles and thereby enhance the rate of reaction and the yield of the product. Further experiments are underway to prove this hypothesis.

12. Conclusion

We have demonstrated the design and feasibility of performing Suzuki coupling reactions using a glass capillary-microreactor with high yields (82–95% in comparison with 11–23% for the conventional method). Either individual or a mixture of reactants can be used in the reactor without compromising the identity or yield of the reaction product(s). The reaction protocol is rapid and could be useful for the qualitative and quantitative determination of novel catalytic reactions. Unlike photolithographic microreactors, our ordinary glass capillary reactors are easily available, affordable, easier to use and the progress of the reaction can be monitored through a variety of techniques, including direct visualization. This approach is useful for designing novel catalysts, reactions and generating new databases for chemical libraries.

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