THE KUMADA-CORRIU CROSS-COUPLING REACTION IN MICRO REACTOR: ADVANTAGES OVER CONVENTIONAL BATCH REACTOR

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SUMMARY

A micro reactor has been used as an alternative to conventional batch reactors for the industrially important Kumada-Corriu cross-coupling reaction of 4-bromoanisole with phenylmagnesium chloride and phenylmagnesium bromide, in the presence of polymer- and silica-supported nickel catalysts. Reasonable conversions could be achieved in a matter of minutes, compared to conversions obtained after 24 h in a conventional batch reactor, albeit on a much smaller scale. The rate constant of the cross-coupling reaction could be increased up to 75 times using the micro reactor, as compared to the batch reaction. The deposition of magnesium species on the surface of the nickel silica catalyst still remains to be solved, while the problem is considerably less serious for the nickel resin catalyst used in the micro reactor system.

I - INTRODUCTION

Reactor miniaturisation, for example micro reactors in which microlitre quantities of reagents are manipulated, has been shown to confer many advantages over conventional laboratory scale chemical apparatus [1]. Micro reactor technology clearly offers considerable advantages in performing safer and more efficient chemical reactions. In particular, the number of compounds that can be prepared and screened can be significantly increased thereby enhancing the discovery phase [2]. Furthermore, the capability of producing a parallel network of micro reactors, the so-called 'scaling-out' of the process, offers a clear route to generating product volume on demand, at the point of use, so reducing the need to store and transport hazardous or highly reactive chemicals [3 - 5]. The technology is still in its early development and it would be presumptuous to expand too far on the potential applications that micro reactors will find, but some early trends are clear. One of the immediate and obvious applications is in combinatorial chemistry and drug discovery, where the generation of compounds with different reagents or under variable conditions is an essential factor [6, 7].

After the first example of organic reactions performed in micro reactors, the number of reactions carried out in these devices has increased dramatically [8 - 10]. However, to date the scope of liquid phase synthesis in micro reactors has, in the majority, been limited to non-metal-catalyzed reactions, with the exception of a few examples of heterogeneous catalysis [11 - 13]. Transition metal-catalyzed cross-coupling reactions have gained popularity over the past thirty years in synthetic chemistry [14]. Numerous reactions have been developed to achieve cross-coupling, of which the Kumada-Corriu reaction is one of the most

efficient ones [15]. We recently reported the immobilisation of a salen-type nickel complex onto a functionalised silica, and its catalytic activity in the Kumada-Corriu reaction performed in a conventional batch reactor and in a micro reactor [16]. In this paper, we wish to report the Kumada-Corriu reaction using the polymer-supported nickel salen-type catalyst in a conventional batch reactor and in an Omnifit micro reactor. The polymer-supported nickel catalyst exhibited better performance in the micro reactor in terms of stability for the system, as compared to the silica-supported one.

II - EXPERIMENT

1. Materials and instrumentation
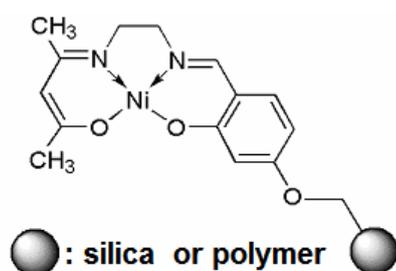
Figure 1: Structure of the supported nickel salen-type catalyst

Chemicals were purchased from Aldrich and Fisher and used as received without further purification. NMR spectra were recorded using a Bruker AC250 spectrometer (^{1}H, 250.1 MHz; ^{13}C, 62.9 MHz) or a Bruker AMX 400 spectrometer (^{1}H, 400.1 MHz; ^{13}C, 100.6 MHz). ^{1}H and ^{13}C chemical shifts were referenced to solvent resonances. GC-MS analyses were performed using a Perkin Elmer GC-MS with a 30 m×0.25 mm×0.25 µm Phenomenex-2B5 column. The polymer- and silica-supported salen-type nickel catalysts were prepared and characterized according to the procedures reported previously [16]. The catalyst loadings of the resin and silica catalysts were 0.5 mmol Ni/g and 0.25 mmol Ni/g, respectively.

2. Conventional batch reaction

Unless otherwise stated, a solution of 4-bromoanisole (0.187 g, 1 mmol) in dry THF (1.5 ml) was added to a Radley's Carousel reaction tube containing the required amount of polymer-supported nickel catalyst (9 mg, 0.5 mol% nickel). The Grignard reagent, phenylmagnesium chloride or phenyl-magnesium bromide (2M, 0.5 ml, 1 mmol) in THF was transferred *via* syringe under a nitrogen atmosphere and added directly into the solution of the organobromide. The mixture was stirred at room temperature for 24 hours under a nitrogen atmosphere. To work-up the reaction, saturated aqueous sodium chloride solution (2 ml) was added. The organic components were extracted into diethyl ether (2×2 ml) which was then dried over anhydrous MgSO$_4$ and the resulting solution analysed by GC and GC-MS with reference to standard solutions of 4-methoxybiphenyl, anisole and 4,4'-dimethoxybiphenyl.

3. Micro flow reaction
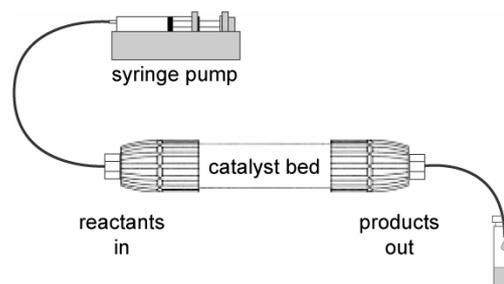
Figure 2: The micro reactor set-up

The Kumada coupling reaction of 4-bromoanisole and phenylmagnesium chloride in THF was carried out in a pressure driven micro flow reactor (length = 25 mm; I.D. = 3 mm) build up from Omnifit glassware (figure 2) containing the silica-supported nickel catalyst (100 mg) or polymer-supported one (60 mg) respectively. A syringe pump (Razel, A-99) was used to drive a pre-determined volume of a mixture of equimolar solutions of 4-bromoanisole and phenylmagnesium chloride or phenylmagnesium bromide in THF (concentration of each component was 0.5 M) through the reactor at known flow rates. The organic components were extracted into diethyl ether and analyzed by GC as described above.

4. Residence time distribution measurement

The mean residence times of reaction solutions within the catalyst bed in the continuous micro flow reactor were measured using the standard experimental method, the step experiment [17]. The outlet absorbance distribution, and hence the outlet concentration distribution, *versus* time was measured online using a fibre optic spectrometer (USB 2000-UV-VIS, Ocean Optics Inc.) at different wavelengths ranging from 450 to 560 nm. Taking into accounts the residence time of the solution in the HPLC standard connectors based on their volumes and the known flow rate (using the equation $t = V/v$, where V is the total volume, v is the flow rate and t is the mean residence time), the mean residence time within the catalyst beds were found to be 6.9 minutes for the silica-supported nickel (figure 3(a)) catalyst and 8.6 minutes for the polymer-supported one (figure 3(b)) at the flow rate of 13 μl/min.
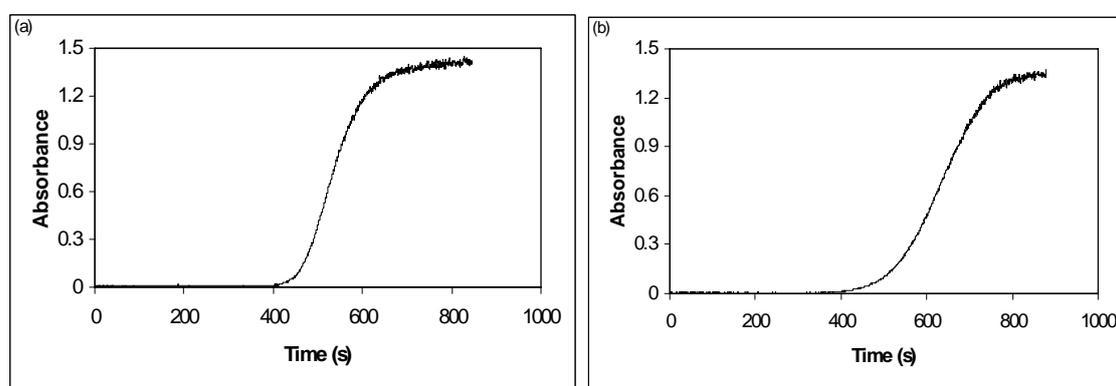
Figure 3: The outlet absorbance distribution *versus* time: (a) for the nickel silica catalyst, (b) for the nickel resin catalyst, at a flow rate of 13 μl/min

III - RESULTS AND DISCUSSION

In this study, the reaction of 4-bromoanisole with phenylmagnesium bromide or phenylmagnesium chloride in tetrahydrofuran (THF) was carried out in a pressure driven micro flow reactor constructed from Omnifit glassware (figure 2). The principal product of the reaction was 4-methoxybiphenyl. However, it was observed that the composition of the final reaction mixture also included anisole and 4,4'-dimethoxybiphenyl and biphenyl as by-products (figure 4). Indeed, the problem of by-product formation involving the Grignard coupling reactions was always encountered in previous publications [18]. Our initial studies focused on the Kumada-Corriu reaction with phenylmagnesium bromide using the nickel resin catalyst of 200 μm in diameter, at the flow rate of 33 μl/min and at room temperature. Samples were collected after 1 h and analyzed as described above. 4-Methoxybiphenyl was formed in a conversion of only 20%, while 67% conversion was observed in the conventional batch reaction. It was found that using the resin support with smaller particle size of 50 μm, the reaction could be considerably improved with the principal product being formed in a conversion of 38%. This can be rationalised by the fact that the number of catalytic sites available for reaction is increased with smaller particle size, due to the increase in catalyst surface area per unit mass. It was, therefore, decided to use the nickel resin catalyst with the average particle size of 50 μm instead of 200 μm for further studies.
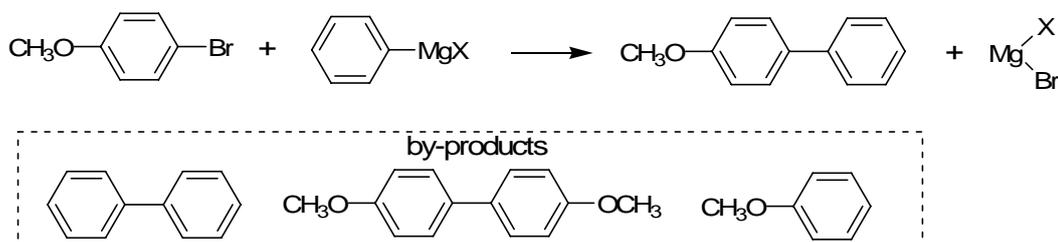
Figure 4: The Kumada-Corriu cross-coupling reaction of 4-bromoanisole with the Grignard reagents
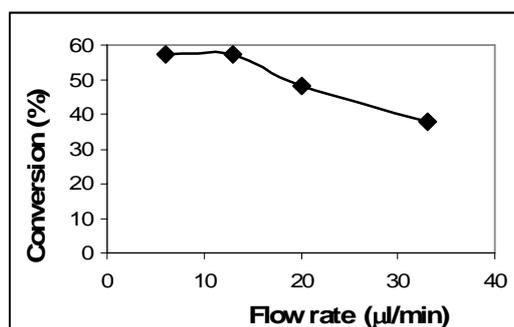
Figure 5: Conversion dependence on flow rates

As the residence time within the continuous reactor has an important effect on the reaction rate, the Kumada-Corriu reaction was then performed at different flow rates. The results of conversion dependence on flow rates are shown in figure 5. The best result was observed using the flow rate of 13 µl/min with 57% conversion to 4-methoxybiphenyl being achieved. This is comparable to conversion observed in the batch reaction. Decreasing the flow rate to less than 13 µl/min was found unnecessary as the conversion to the principal product did not increase any further. Increasing the flow rate to more than 13 µl/min resulted in a drop in conversion, with 48% and 38% conversion to 4-methoxybiphenyl being achieved at the flow rate of 20 µl/min and 33 µl/min, respectively. Since the reaction conditions such as concentration, ratio of phenylmagnesium bromide to 4-bromoanisole, solvent and temperature remained unchanged in all cases, the observed increase in conversion, when decreasing the flow rate of the system, was due to an effective increase in residence time within

the continuous reactor and hence an increase in contact time between the catalyst and the reagents.

The common prejudice against microreactors is the danger of blockage. It was found that the reaction of 4-bromoanisole and phenylmagnesium bromide using the nickel resin catalyst produced a large amount of $MgBr_2$ and that this precipitate caused blockages in the reactor after only 1 h. By changing the Grignard reagent, from the bromide to the chloride (PhMgCl instead of PhMgBr), the reaction could be improved without any precipitate being observed during the course of the reaction. It should be noted that MgBrCl is considerably more soluble in THF than $MgBr_2$. The absence of any precipitate using the PhMgCl reagent is critical for use in a micro flow reactor since any precipitation would cause blockages in the reactor. Phenylmagnesium chloride was therefore used for all subsequent reactions. The micro reactor was then filled with the nickel resin and silica catalysts respectively, and run for 5 h at the flow rate of 13 µl/min with

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product samples being collected every hour. It should be noted that in a typical run, the reactor was filled with approximately 100 mg nickel silica while only 60 mg nickel resin was used, although there was not much difference in the total amount of the nickel. Using the chloride Grignard, the nickel resin-catalyzed continuous reaction could afford the desired product (4-methoxybiphenyl) in a conversion of up to 69%, which is higher than the conversion observed for the reaction using phenylmagnesium bromide, and higher than that observed for the nickel silica-catalyzed continuous reaction. Furthermore, the conversion almost remained unchanged within 5 h, while the micro reactor system using the nickel silica catalyst showed a gradual degradation in performance with a conversion of only 30% being achieved after 5 h (figure 6). This means that although no precipitate was visually observed, deposition of salts (MgBrCl, $MgBr_2$) on the surface of the silica-supported

catalyst, still occurred, making active sites less accessible from reactants. The problem was considerably less serious for the nickel resin catalyst used in the micro reactor system.
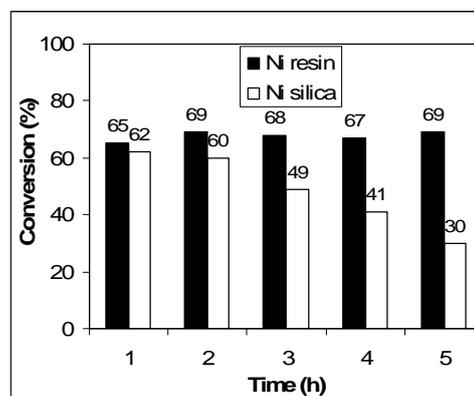
Figure 6: Comparison of conversion of nickel silica-catalyzed continuous reaction *vs.* nickel polymer-catalyzed continuous reaction
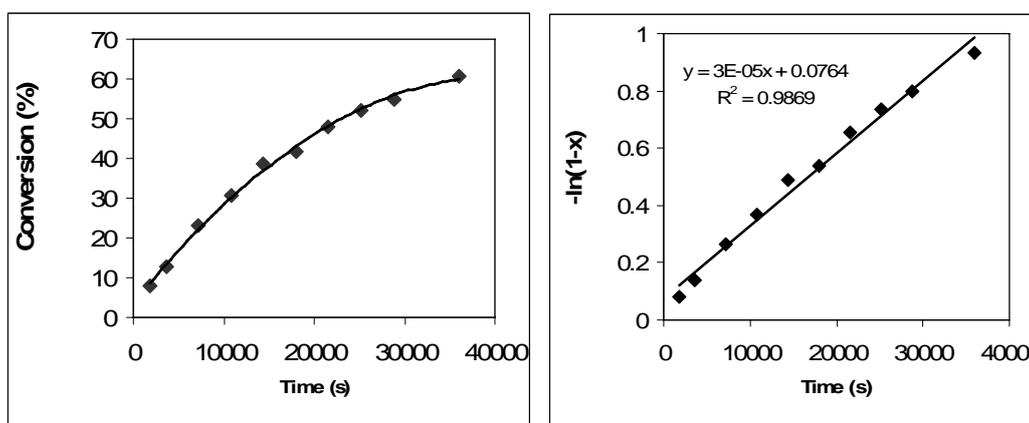
Figure 7: Kinetic data of the Kumada reaction (batch) using the nickel resin catalyst, showing an observed *pseudo* first order rate constant of $3 \times 10^{-5}\,s^{-1}$

$$k_{obs} = -[\ln(1-x)] \times 1/t \qquad (1)$$

Enhanced reaction rates were observed using micro reactor technology, compared with those achieved using conventional techniques. We therefore decided to investigate the enhancement of the observed rate constant of the continuous flow reaction, compared with that of the batch reaction. For the batch reaction using the polymer-supported catalyst, aliquots

were withdrawn at different time intervals to measure the corresponding conversion. The data were then analyzed using the design equation 1 [16], where x is the mole fraction of 4-methoxybiphenyl produced, t is the corresponding reaction time. The mechanism of the overall reaction, and hence the order of the individual elementary reactions in the catalytic cycle is complex and still remains to be elucidated. However, the cross-coupling

reaction to form 4-methoxybiphenyl was shown to be *pseudo* first order with respect to the starting bromide giving the observed rate constant of $3 \times 10^{-5}.s^{-1}$ for the nickel resin-catalysed reaction (figure 7), which is comparable to that of the previous report.

The continuous reaction is also assumed to be first order because the mechanism in batch and flow modes are the same, so comparisons were made using this assumption. Since the total reactor volume is still unknown, the mean residence time within the nickel resin catalyst bed in the micro reactor was therefore measured using the standard experimental method, giving a period of 8.6 minutes at the flow rate of 13 µl/min. It should be noted that in a continuous flow reactor, the mean residence time is also the contact time and that the residence time in the micro reactor is much shorter than in the batch process. This means that the observed rate constant of the cross-coupling reaction to form 4-methoxybiphenyl was considerably faster, with $k_{obs} = 2.3 \times 10^{-3}$ s^{-1}, using the micro reactor system. This represents an enhancement of reaction rate of 75 times as compared to the batch reaction.

The micro flow reaction system clearly offers advantages over the conventional batch reaction. The enhanced reaction rate means that yields obtained after 24 h in a batch reaction could be realised in a matter of minutes using the micro flow reactor system, albeit on a much smaller scale. This can be rationalised in terms of the number of catalytic sites available at which reaction can occur. In a stirred batch reactor, although the nickel resin catalyst has high surface areas due to the swelling behaviour of the resin in THF, reaction occurs essentially at the external surface of the support, since the penetration of the reagents to interior catalytic sites is governed by a slow diffusion process. In the constraints of the micro reactor, where the nickel catalyst is packed into the Omnifit tubing, the reaction solution is driven through the pores under pressure and the number of catalytic sites available for reaction is increased. Moreover, in the flow reactor a small amount of substrate is forced into intimate contact with a large amount of catalyst. With the nickel resin

system using a flow rate of 13 µl/min, 1.34 mmol (246 mg) of 4-methoxybiphenyl was produced in 5 h. By scaling out the system, it can be envisaged that yields of synthetic method could be readily achieved. For example, 100 micro reactors in parallel would produce more than 24 g of the desired product in the same time interval.

IV - CONCLUSIONS

In summary, the Kumada-Corriu reaction using the polymer-supported nickel catalyst at room temperature was readily carried out in a continuous micro flow reactor. Reasonable conversions could be achieved in a matter of minutes, compared to conversions obtained after 24 h in a conventional batch reaction, albeit on a much smaller scale. Comparison of the reaction rates from continuous flow and batch reactions gave an enhancement of the reaction rate of 75 times for the cross-coupling reaction to form 4-methoxybiphenyl using the micro flow reactor. The deposition of magnesium species on the surface of the nickel silica catalyst still remains to be solved, while the problem is considerably less serious for the nickel resin catalyst. Although simple in design and concept, with easily replaceable catalyst beds and interchangeable reagents premixes, the micro flow reactor system provides a powerful tool in catalyst screening and a route to high throughput synthesis. By scaling out the system, it is easily seen that yields of synthetic value can readily be achieved. Products can be generated on demand, at the point of use, so reducing the need to store and transport hazardous chemicals. Therefore, the micro reactor is ideal for the rapid production of small inventories of reagents and for the rapid screening of solid catalysts due to their ease of addition to and removal from the reactor.

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