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Development of a Grignard-Type Reaction for Manufacturing in a Continuous-Flow Reactor

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ABSTRACT: This paper describes the scale-up of a highly exothermic and fast reaction from a microreactor with an internal volume of less than 1 mL to a mesoreactor with an internal volume of 13.5 mL. The development of a continuous process for manufacturing a ketone from an ester using a Grignard reagent is described. The different steps undertaken and the considerations made to be able to operate in continuous mode and achieve a product output of ca. 0.5 kg are presented.

INTRODUCTION

Herein we describe a simple approach for the development and scale-up of a Grignard reaction realizing the opportunity offered by micro- and mesoreactors. It also includes the ways in which significant challenges posed by precipitation and fast and highly exothermic reactions were addressed. The chemical transformation under consideration is a Grignard reaction where an ester starting material **1** is subjected to a Grignard reagent leading to the formation of ketone **2** (Scheme 1). Ketone **2** is an intermediate in the synthesis of drug candidates in the early development phase.

The chemistry described in this paper was originally developed for processing in a batch reactor following the protocol developed by Ikuo and Tadahika.[1] This procedure consumes 2 equiv of MeMgBr in combination with 6 equiv of triethylamine in order to generate the enolate form in situ, which avoids further reaction of ketone **2** with excess MeMgBr leading to tertiary alcohol **3**. Quenching of the reaction with acid gives a mixture of ketone **2** and the aldol condensation product **4**. In the original procedure, this mixture was treated with sodium hydroxide at 45 °C to promote the retro-Aldol reaction, giving ketone **2** as the sole product. However, this approach was not viable in our specific case since **2** decomposed under basic conditions at elevated temperature. Medicinal chemistry experience indicated that the formation of aldol **4** could not be controlled when the reaction was performed in a 100 mL round-bottom flask. It was noted that the results fluctuated dramatically with isolated yields of **2** from 30% to 60% and with **4** as the main by-product. Residual ester **1** and tertiary alcohol **3** contributed less than 10% of the total amount of product. The aldol product **4** inhibited crystallization of ketone **2**, and chromatography was required to obtain the desired quality.

Continuous-flow micro- or mesoreactors have a superior surface-area-to-volume ratio and hence an improved heat transfer capacity compared with conventional batch reactors.[2] This offers advantages such as the possibility of maintaining temperature control even when the reaction in question is fast and highly endo- or exothermic. Furthermore, since the reactors have a well-defined working volume, the reaction (residence) time can be accurately controlled by adjustment of the flow rate(s). These possibilities frequently result in better reaction profiles and increased yields. Thus, the use of continuous processing can lead to distinct improvements in efficiency that, for obvious reasons, provide an added value to the fine chemicals and pharmaceutical industries. To date, several examples using microreactors have been reported in the literature, including DIBAL-H reductions[3] and organometallic reactions.[4]

RESULTS AND DISCUSSION

In this specific case, it was realized that the use of a flow reactor could potentially decrease the amount of unwanted aldol product **4**. Indeed, this technology opens the opportunity to have a more rapid quench reaction because of more efficient addition of acid.

Two different systems were used to investigate the reaction. For early screening, a Sigma-Aldrich glass chip with an internal volume of 630 μL (Figure 1a) was used. For further development, an ART PR37 reactor, designed by Alfa Laval AB (Figure 1b),[5] was used. This can be equipped with plates with different channel sizes.[6]

The reaction was initially screened to understand the influence of temperature and amount of reactant on the product distribution between unreacted starting material **1**, the desired ketone **2**, tertiary alcohol **3**, and aldol product **4**. The initial screening was made in a simple setup using a double syringe pump imposing identical flow rates connected to a Sigma-Aldrich glass chip (Figure 1a). Furthermore, the reaction was quenched in a semibatch mode by collecting the discharge from the flow reactor into a large excess of acid at 0 °C. The procedure from Ikuo and Tadahika[1] was followed by mixing the Grignard reagent with Et_3N prior to the reaction. One syringe

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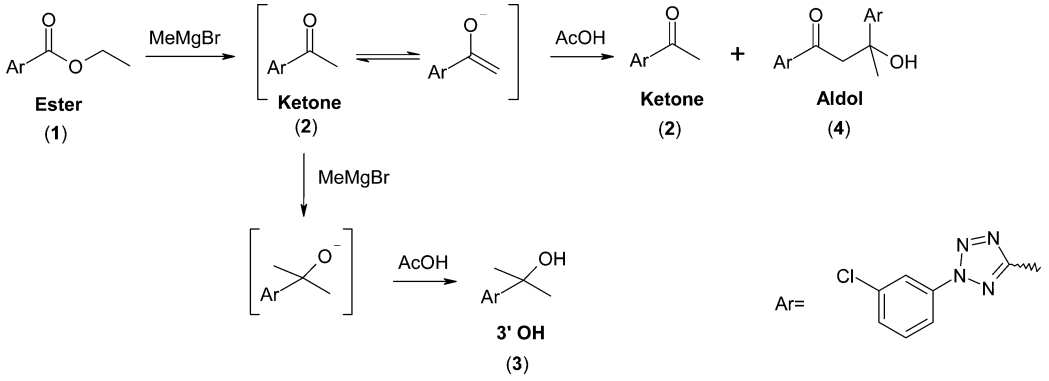
Scheme 1. Ester 1 is reacted with MeMgBr, leading to the formation of ketone 2, which can undergo various transformations to generate compounds 3 and 4



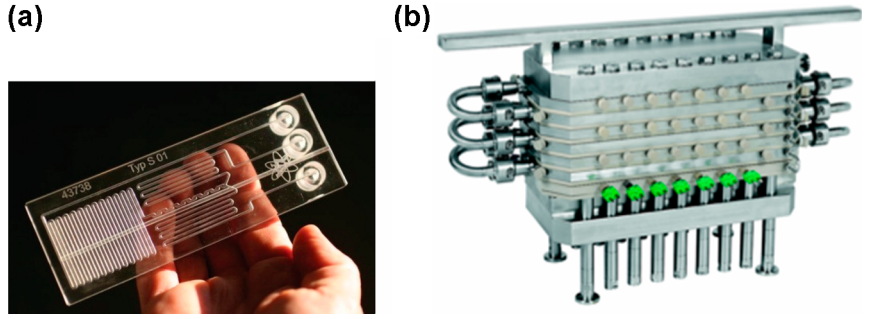


Figure 1. Pictures of (a) the Sigma-Aldrich glass chip and (b) the ART PR37 reactor.

was loaded with a solution of ester **1** in 2-MeTHF at different concentrations (see Table 1). The other syringe was loaded with a solution of MeMgBr and Et_3N in toluene/2-MeTHF. The different amounts of the Grignard reagent and Et_3N were obtained by varying the concentrations of the reagents loaded in the syringes.

First, the amount of MeMgBr was varied from 1.2 to 1.5 equiv (Table 1, entries 1−3). Increasing the amount of MeMgBr resulted in better conversion (less of the unreacted ester **1**) but at the cost of more tertiary alcohol **3**. It could be concluded that 1.5 equiv of MeMgBr was the upper limit to be used since the yield of tertiary alcohol **3** was already at 14%. Shortening the reaction time from 13 to 6 s while keeping the temperature at 0 °C (entry 4) gave better conversion of ester **1** (but within experimental error) while maintaining the amounts of tertiary alcohol **3** and aldol **4**. However, reducing the reaction temperature to −20 °C (entries 5 and 6) did not give any significant advantages. Increasing the concentration of the ester **1** solution from 0.6 to 0.8 M (entry 7) resulted in an unstable system and blockage due to precipitation before steady state could be reached and any sample could be collected. Replacing Et_3N with TMEDA (entry 8) gave poor results with low conversion and over-reaction to giv the tertiary alcohol.

Table 1. Results of the screening using the Sigma-Aldrich glass chip and a semibatch quench

	equivalents of				HPLC yield (area %)			
entry	MeMgBr	Et_3N	t (s)[a]	T (°C)	**1**	**2**	**3**	**4**
1[b]	1.2	3.6	13	0	9	80	6	5
2[b]	1.4	4.2	13	0	9	79	7	5
3[b]	1.5	4.5	13	0	1	76	14	9
4[b]	1.4	5.2	6	0	3	85	7	5
5[b]	1.3	4.0	13	−20	5	80	11	4
6[c]	1.3	4.0	13	−20	5	80	11	4
7[d]	1.1	3.4	13	0	no sample could be taken			
8[e]	1.4	4.6[c]	13	0	26	43	23	8

[a]Time in the chip reactor. [b]HOAc/H_2O/MeTHF quench. [c]Acetic acid quench. [d]0.8 M in **1** and 1 M HCl(aq)/2-MeTHF quench. [e]TMEDA as an additive and HOAc/2-MeTHF quench.

Shortening the residence time gave a similar reaction outcome but better throughput (vide supra). Therefore, the conditions given in Table 1 entry 4 were used to convert 160 g of ester **1** to 100 g of ketone **2** (after chromatography), corresponding to an isolated yield of 68% after 5.5 h of processing in the chip reactor.

This initial screening encouraged us to further optimize the process to identify conditions suitable for manufacture of larger amounts. To increase the throughput of the process, it was decided to further investigate some parameters such as the quenching procedure, flow rate and the composition of the starting solution. For simplicity it was decided that the Et_3N would be mixed with the solution of ester **1** instead of using the original procedure.[1]

The ART PR37 reactor offered opportunities to add an additional solution to quench the reaction while maintaining full temperature control. The larger volume of this reactor also made it possible to use a higher flow rate. To avoid the formation of a large amount of triethylammonium salt, it was decided to quench the reaction in situ with as small an excess of acid as possible. Therefore, it was attempted to quench the reaction with 1.2 equiv of pure acetic acid and also 1.2 equiv of HCl in an aqueous solution (Table 2, entries 1 and 2). Both solutions resulted in immediate clogging of the reactor. In the

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Table 2. Results of the screening using the ART PR37 reactor with different plate volumes at 0°C

				HPLC yield (area%)			
entry	ART plate size (PL37/X-X-C22)	equiv of MeMgBr	residence time (s)	1	2	3	4
1[a]	0.8-2.2	1.2	20	2.9	22.3	4.1	70.7
2[b]	0.8-2.2	1.2	20		no sample could be taken		
3[c]	0.8-2.2	1.2	20	1.5	93	4	1.5
4[c]	3-12	1.4	24	0	85.1	12.8	2.1

[a]Quench in the ART PR37 with 1.2 equiv of pure acetic acid. [b]Quench in the ART PR37 with 1.2 equiv of HCl. [c]Quench in the ART PR37 with a equivolume solution of acetic acid, water, and 2-MeTHF (1:1:1 v/v/v, 15.6 equiv of AcOH).

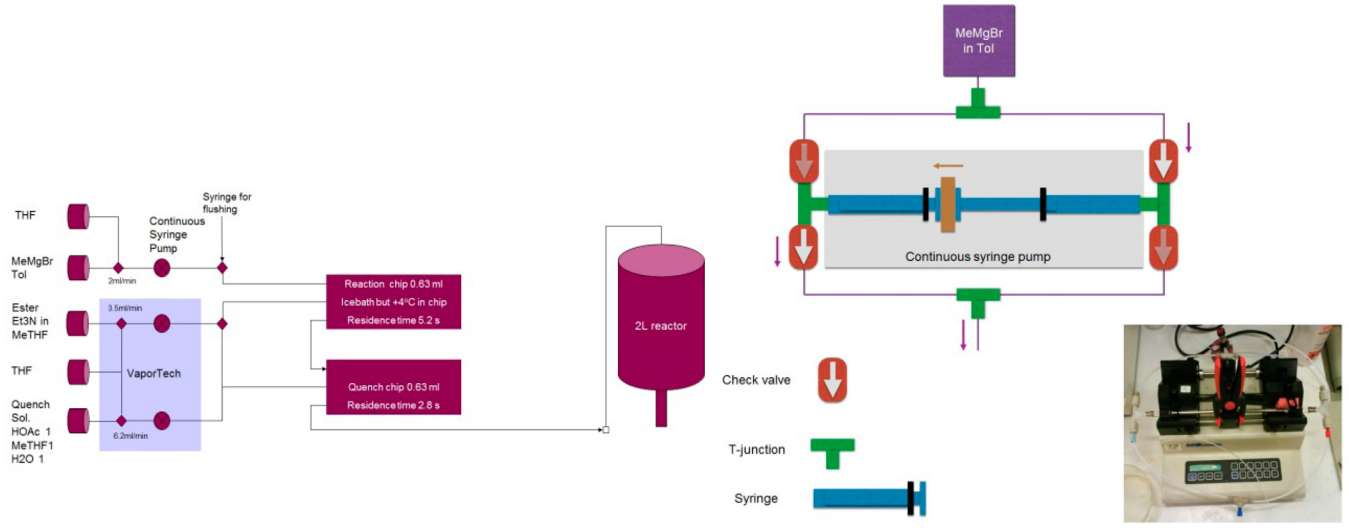

Figure 2. Schematic setup for the continuous processing in the Aldrich chip reactor and continuous syringe pump.

first case (entry 1), a sample could be taken, and it showed a significant increase in the yield of aldol product **4** (up to 71%).

From earlier experiments it was known that quenching the reaction with a equivolume mixture of acetic acid, water, and 2-MeTHF (one-phase solution) resulted in a clear solution. It was therefore decided to implement this quenching in the flow reactor using a 1:1:1 (v/v/v) mixture of acetic acid, water, and 2-MeTHF (Table 2 entry 3). This approach solved the precipitation issue and gave significantly better results with higher conversion and better selectivity. These results indicated that a practical approach was to mix Et_3N with ester **1** and react it with 1.2 equiv of MeMgBr at 0 °C for 20 s before quenching the reaction at 0 °C with a 1:1:1 (v/v/v) mixture of acetic acid, water and 2-MeTHF.

In order to rapidly convert the 580 g of ester **1** needed for the next campaign, the reaction was scaled up by using the ART PR37 reactor (Figure 1b) equipped with a plate of larger internal volume so that the total flow rate could be increased from 7 to 25 mL/min while keeping a similar residence time. The amount of MeMgBr was also increased to 1.4 equiv (Table 2, entry 4) to ensure complete reaction. This was based on strategic judgment, as it was known that the residual tertiary alcohol **3** did not compromise the crystallization of ketone **2** while unreacted ester **1** had been observed to create issues at a later stage in the reaction sequence.

On the basis of the above results, the reaction conditions from Table 2, entry 4 were chosen to manufacture the required amount of ketone **2**. During the continuous processing of 580 g of ester **1**, precipitation occurred, as evidenced by a pressure increase that soon resulted in a blockage of the reactor. This necessitated the implementation of a cleaning cycle using the quench solution to back-flush the system when the pressure was above 5 bar. The cleaning cycle was repeated every 45 min, and the process was restarted after every such cycle. Since the cleaning procedure and restart was not fully optimized this caused loss of material, resulting in a total yield of less than 50% even though the conversion reflected the results in Table 2, entry 4.

More material of the API and ketone **2** was required for extended toxicity studies, but as the ART PR37 setup was not available, a system based on Aldrich chip reactors (Figure 1a) was designed. To accommodate an in situ quench, two glass chip reactors from Sigma-Aldrich (Figure 1a) were used. The first one was used to add the Grignard reagent, and the second one was employed to quench the reaction (Figure 2). A modified Vapourtec R-Series reactor system was used to feed both the ester **1**/Et_3N solution and the quench solution. The Grignard reagent solution was fed by a double syringe pump fitted with two 2.5 mL gastight syringes. By means of a combination of check valves, when one syringe was adding the Grignard solution the other syringe was refilled, and therefore, the syringe pump could be used to continuously feed the solution containing the Grignard reagents (Figure 2). The injection loop of the Vapourtec reactor was used to introduce the wash solution when the pressure rose above 5 bar. The ester **1** solution (0.46 M in 2-MeTHF with 3.5 equiv of Et_3N) and the MeMgBr solution (1.4 M in toluene/THF from Aldrich) were reacted in the first chip reactor immersed into an ice bath after a short precooling path in the chip. The process stream was then immediately quenched in the second chip (also immersed in an ice bath at 0 °C) by reaction with 1:1:1 (v/v/v) HOAc/water/2-MeTHF. Finally, the process stream

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was collected in a batch reactor containing toluene and brine at 10 °C (Figure 2). Monitoring of the temperature in the chip with a Pt100 sensor showed that without stirring in the ice bath, the temperature in the chip reached 8 °C within 5 min.

Knowledge accumulated from earlier development indicated that a short residence time would give an acceptable reaction profile and reasonable throughput. The plan was to use between 1.2 and 1.7 equiv of MeMgBr. A key objective, as mentioned before, was to keep the residual ester **1** and aldol condensation product **4** at a low level (<1%). As can been seen in Table 3, entry 3, this requirement was fulfilled when 1.7 equiv of MeMgBr was used.

Table 3. Results of the screening using different ratios of MeMgBr and residence times in two Sigma-Aldrich chip reactors

		residence time (s)		HPLC yield (area%)			
entry	equiv of MeMgBr	chip 1	chip 2	**1**	**2**	**3**	**4**
1	1.2	5.4	2.8	10	85	5	<1
2	1.5	6.3	3.0	5	87	7	<1
3	1.7	6.9	3.2	<1	90	10	<1

Under the reaction conditions depicted in Table 3, entry 3, 300 g of ester **1** could be converted within 12 h. After separation of the collected process stream and washing once with brine, the organic phase was evaporated to dryness and was then crystallized from 2:1 IPA/water to give ketone **2** in 63% isolated yield (167 g). A final crop of 25 g was isolated after chromatographic purification of the mother liquor, giving a total yield of 72%. Similar issues with precipitation occurred during this manufacture, and the cleaning cycle was run every 45 min. As can be observed in Figure 3, the precipitation occurred right after the mixing zone.

CONCLUSION

The formation of by-product **4** could be suppressed below 1% by quenching the reaction in the flow reactor. The procedure developed for the flow reactor requires less than 2 equiv of MeMgBr, representing an improvement compared with the original procedure of Ikuo and Tadahika,[1] which required 2 equiv of MeMgBr. However, to reach full conversion of ester **1**, a small excess of Grignard reagent (1.2−1.7 equiv) had to be used. This excess led to a minor loss of yield at the cost of tertiary alcohol **3**, but this was a minor issue for the overall process. The residence time could be reduced to less than 7 s, allowing good productivity for this process in a microreactor (300 g of ester in 12 h).

On the basis of measurements of the temperature in the chip, this reaction appears to be highly exothermic and could be expected to cause processing issues if scaled up in a conventional stirred batch reactor.

It has been demonstrated that such a challenging reaction is not sensitive to the type of flow reactor used, since similar results were obtained in both the Sigma-Aldrich glass chip reactor and in the ART PR37 plate reactor with two different channel sizes and geometries. The difference in residence time (7 s vs 20 s) in the addition step indicates that the initially formed complex is formed quickly and is stable enough at the reaction temperature.

This procedure can be used as an alternative to the Weinreb ketone synthesis and reduces the synthesis by at least one step (synthesis of the Weinreb amide).

EXPERIMENTAL SECTION

Ketone 2, Method 1. *Solution A.* Ethyl 2-(3-chlorophenyl)-2*H*-tetrazole-5-carboxylate (**1**) (75.3 g, 0.30 mol) was dissolved in 2-MeTHF (430 mL), and the resulting solution was filtered to give a 0.6 M solution.

Solution B. MeMgBr (123 mL, 1.4 M in toluene/THF) was mixed with Et_3N (87 mL, 1.17 mol).

Solution C. The quench solution was made of equal volumes of acetic acid, water, and 2-MeTHF.

Example Procedure (Table 1, entry 4). Solutions A and B were charged at a flow rate of 3 mL/min each into the Sigma-Aldrich glass chip at 0 °C, and the discharge was collected in a vessel containing stirred solution C.

Ketone 2, Method 2. *Solution A.* Ethyl 2-(3-chlorophenyl)-2*H*-tetrazole-5-carboxylate (**1**) (301 g, 1.19 mol) was dissolved in 2-MeTHF, and Et_3N (0.58 L, 4.17 mol) was added. The resulting solution was filtered and then diluted to a total volume of 2.59 L, giving an ester **1** concentration of 0.46 M.

Solution B. MeMgBr (Aldrich, 1.4 M in toluene/THF) was used as supplied.

Solution C. The quench solution was made of equal volumes of acetic acid, water, and 2-MeTHF.

Example Procedure (Table 2, entry 3). Solutions A, B, and C were charged at flow rates of 5, 2, and 6.2 mL/min, respectively.

Example Procedure (Table 2, entry 4). Solutions A, B, and C were charged at flow rates of 17.9, 8.0, and 22.1 mL/min, respectively.

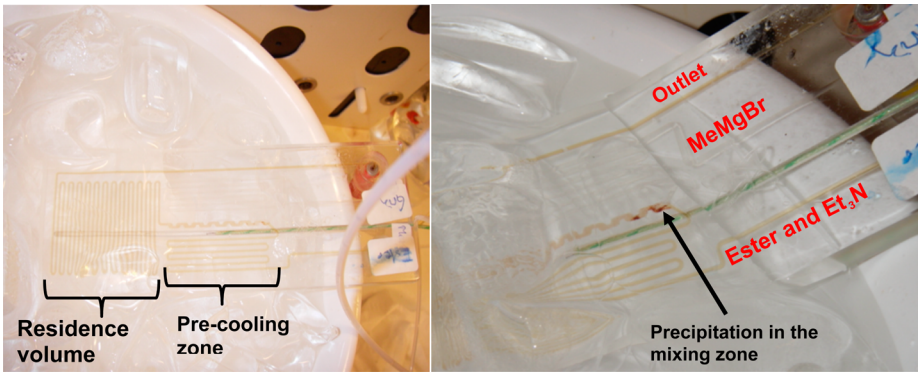

Figure 3. Picture of the Sigma-Aldrich glass chip reactor used for the mixing of MeMgBr and solution of ester **1**/Et_3N.

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Example Procedure (Table 3, entry 3). Solutions A, B, and C were charged at flow rates of 3.5, 2.0, and 6.2 mL/min, respectively.

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Notes

The authors declare no competing financial interest.

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(5) The ART PR37 plate reactor consists of a series of cassettes. The core of each of these is a specially designed process channel plate into which the process and utility channels are machined. These are designed to promote optimum mixing and heat transfer performance. Different numbers of these cassettes can be stacked vertically and held together in a frame. The reactor frame holds the plates together in compression, thus sealing the fluid channels. This frame is spring-loaded, which ensures that the correct sealing force is maintained at all times, even when extreme temperatures are involved.

(6) Each plate has one process inlet and one process outlet port. Secondary ports that make it possible to add specific reactants or to insert measuring and monitoring devices are positioned along the length of the plate and provide access to the main process channel. The process channels are connected in series to ensure the required residence time. Four different sizes are available and fit in the PR37 reactor frame: PL37\0.8-2.2-C22 (volume per plate = 3.5 mL; cross section: min = 0.85 mm^2, max = 1.8 mm^2); PL37\3-12-C22 (volume per plate = 13.6 mL; cross section: min = 3 mm^2, max = 6 mm^2); PL37\12-46-C22 (volume per plate = 24.9 mL; cross section: min = 6 mm^2, max = 12 mm^2); PL37\12-46-C22 (volume per plate = 47.7 mL; cross section: min = 12 mm^2, max = 24 mm^2).