Asia Flow Chemistry System

Flow Chemistry – Continuous Flow Synthesis of Carboxylic Acids from Grignard Reagents with Carbon Dioxide Gas

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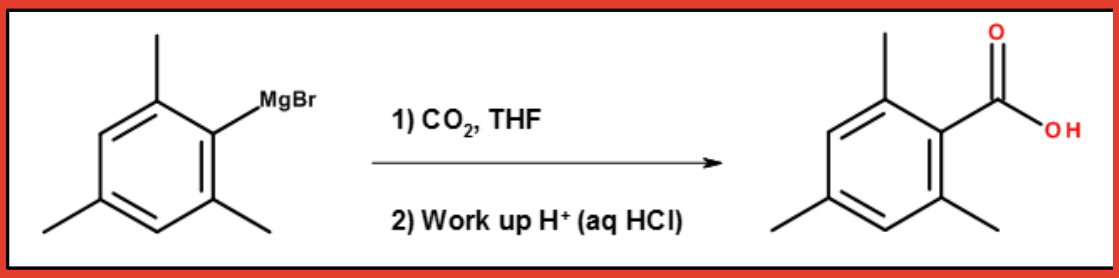
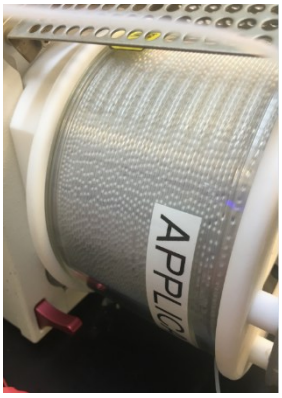


Summary

This application note demonstrates how to perform gas-liquid flow chemistry reaction on the Asia Flow Chemistry System. The reaction used as an example is the continuous flow synthesis of Carboxylic Acids from Grignard Reagents with Carbon Dioxide gas.

Using the 1000ul glass microreactor at a combined flow rate of 150ul/min with gas pressure set to 0.5bar above system pressure (2 bar) full conversion to the acid was observed by TLC. The full quantitative conversion was observed up to a combined flow rate of 750ul/min after which the conversion began to drop off.



Using a 4ml fluoropolymer tube reactor we repeated the experimental conditions set out above. At combined flow rates below 1000ul/min with a gas pressure maintained 0.5bar above system pressure (2 bar) a full conversion was observed.

The Asia Flow Chemistry System provides an easy-to-use, safe, continuous method for the introduction of reactive gases in a liquid/gas plug-flow method under anhydrous conditions.

Introduction

The use of flow chemistry methods in the synthesis of chemical compounds is well documented to give a wide range of benefits over traditional batch methods. The use of reactive gases under these conditions is not so readily explored however. The use of reactive gases in research laboratories is often under used due to issues with safety concerns, the containment of pressurized gases and associated costs of scaling up these reactions.

The use of flow chemistry methods can overcome these problems often giving cleaner reactions, increased cost efficiency and ease of work-up.

Reaction Mechanism Nucleophilic Addition of RMgX to Carbon Dioxide

Step 1:
The nucleophilic **C** in the Grignard reagent adds to the electrophilic **C** in the polar carbonyl group, electrons from the **C=O** move to the electronegative **O** creating an intermediate magnesium carboxylate complex.

Step 2:
The work-up step is a simple acid/base reaction. Protonation of the carboxylate oxygen creates the carboxylic acid product from the intermediate complex.

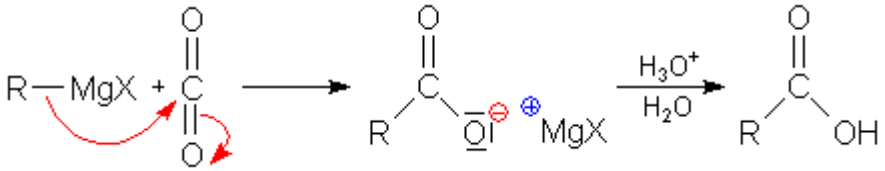


Figure 1: *Reaction Mechanism Nucleophilic Addition of RMgX to Carbon Dioxide*

This chemistry has been successfully adapted from the research carried out by Prof. Steven Ley at Cambridge University*.

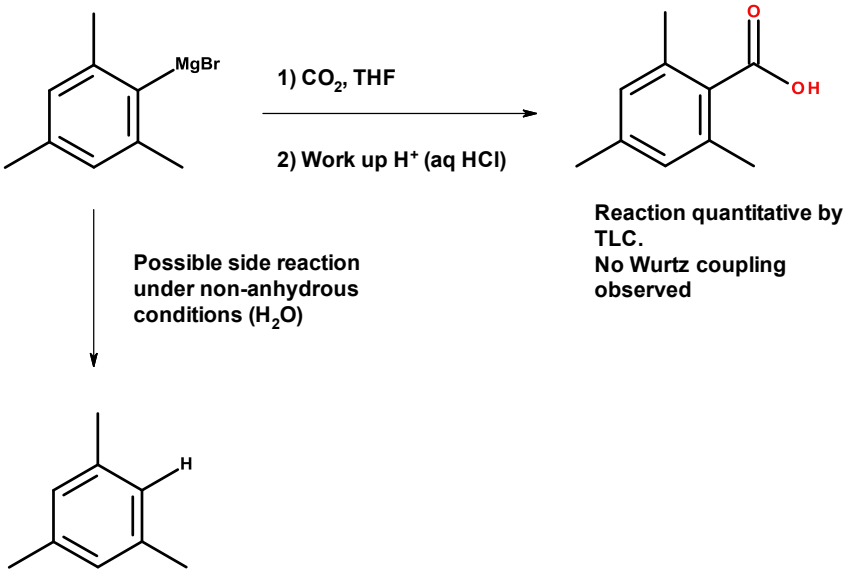


Figure 2: *Synthesis of Carboxylic Acids from Grignard Reagents with Carbon Dioxide gas*

Materials and methods

The experiment uses the Asia Flow Chemistry System with the addition of a gas regulator to control the flow of the reactive carbon dioxide gas (CO_2) into either a glass microreactor or a fluoropolymer tube reactor.

System Setup

The Asia system used in this experiment uses the following modules;

- Asia Pressurized Input Store (part number 2200400)
- Asia Pump (part number 2200292)
- Asia Reagent Injector fitted with 5ml Sample Loops (part number 2200520)
- Asia Chip Climate Controller (part number 2200526)

* Anastasios Polyzos, Matthew OBrien, Trine P. Petersen, Ian R. Baxendale, and Steven V. Ley, The Continuous-Flow Synthesis of Carboxylic Acids using CO2 in a Tube-In-Tube Gas Permeable Membrane Reactor, Angew. Chem. Int. Ed. 2011, 50, 1190 –1193.

- Asia Pressure Controller (part number 2200532)

NOTE: The introduction of carbon dioxide gas was controlled via a CO_2 specific gas regulator. The regulator used needs to have pressure control of at least 0.5bar to allow the fine control of gas input.

NOTE: Care is needed when using CO_2 gas, ensure that all experiments are carried out in an adequate fume cupboard in a well ventilated environment.

The excess CO_2 eleuted from the reactor was scrubbed in an saturated aqueous NaOH solution.

Schematic of Setup

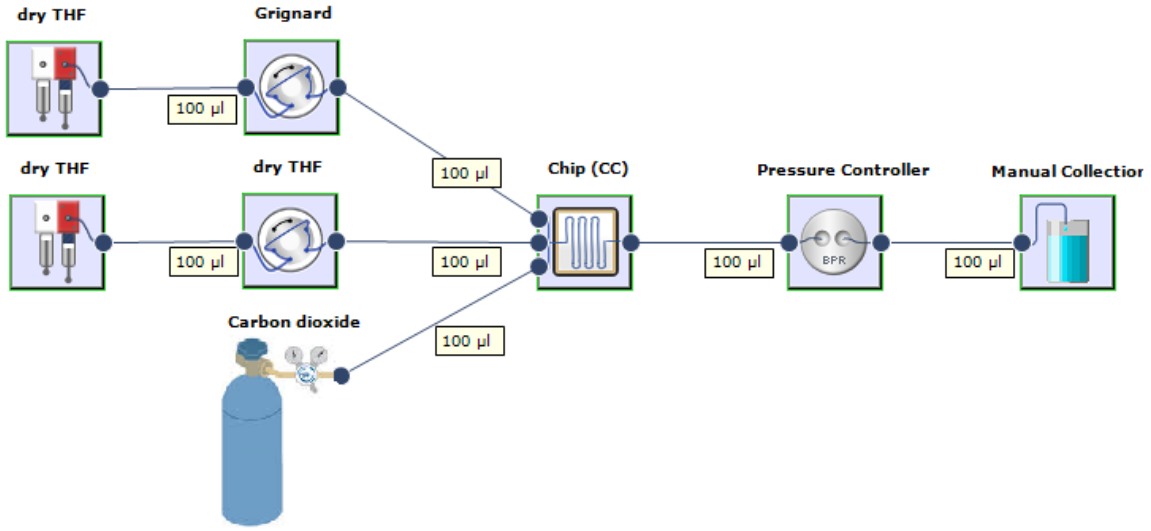


Figure 3: *Fluidic Setup for Synthesis of Carboxylic Acids using Carbon Dioxide gas*

Figure 4: *Asia Discovery System used in Gas/Liquid Application*

Reagent Preparation

For this reaction the following chemicals are needed:

- 2-Mesitylmagnesium bromide solution (1.0M in THF) (CAS: 2633-66-1)
- Hydrochloric acid solution (0.1M) (CAS: 7647-01-0)
- Sodium hydroxide solution (CAS: 1310-73-2)
- Dry tetrahydrofuran (CAS: 109-99-9)

The Grignard reagent solution was used as supplied.

NOTE: An equal volume of dry THF was introduced via the second sample loop of the Reagent Injector to dilute the Grignard solution to 0.5M in-situ.

System Parameters

System Solvent: dry tetrahydrofuran

Reagent A: 2-Mesitylmagnesium bromide solution (1.0M in THF)

Reagent B: Dry tetrahydrofuran

Flow Rate A: variable (50 – 250 µL/min)

Flow Rate B: variable (50 – 250 µL/min)

Stochiometry Reagent A:Reagent B 1:1

Gas Pressure: 0.5 - 15bar

Reactor Volume: 1000µL glass microreactor / 4ml fluoropolymer tube reactor

Reactor Temperature: 25°C

Back Pressure regulator: 1 - 20bar

Method

Prior to the reaction being performed it is essential that the system is completely dry to prevent any possible decomposition of the reagents and limit possible side-reactions. Hydrolysis of the Grignard reagent produces insoluble salts that may result in clogging within the system.

1. Fill the solvent bottles with dry methanol and place the bottles on the pressurized input store under an inert gas atmosphere (nitrogen).
2. Flow dry methanol through the complete system at 1.0ml/min for at least 5 mins.
3. Replace the solvent bottles with dry tetrahydrofuran and repeat step 2.
4. Repeat steps 1-3 finishing with the system completely primed with dry tetrahydrofuran.

Once the system is fully primed with dry solvent and no leaks are detected the reaction can be performed. The following sequence of events was carried out for each reaction:

1. Sample Loading: Both valves on the Asia Reagent Injector were set to ‘Fill’ and Reagent A and Reagent B solutions were injected into the 5ml sample loops.

2. Set System Parameters: The reaction was run under Manual control under the following reaction conditions set.

    a. Flow Rates: The desired flow rate was entered into the Asia Pump, note the flow rate for each channel was the same to ensure a constant 2 fold dilution of the Grignard reagent.
    b. Temperature:
        i. When the glass microreactor was used, a temperature of 25°C was set on the Asia Chip Climate Controller
        ii. When the fluoropolymer tube reactor was used, no temperature was set (ambient temperature was used).
    c. System Pressure: A range of system pressures was explored ranging from 2 – 15 bar. The pressure was set using the Asia Pressure Controller.
    d. CO_2 Gas Pressure: The CO_2 gas pressure was set to ~0.5bar above that of the system pressure.

NOTE: : Note: The gas pressure determines the amount of gas introduced into the reaction. At ~0.5 bar above system pressure an equal volume of gas/liquid is observed as consecutive phases. Increasing the gas pressure will result in an increased ratio of gas:liquid and decreasing the gas pressure will result in a decreased ratio.

3. Reagent Injection: When the desired ratio of gas:liquid is obtained (this may take a period of time to stabilise) the reagents were introduced into the flowing stream by switching the Asia Reagent Injector valves to 'Inject'.

4. Work-Up and Analysis: The collection stream was directed into a sealed bottle containing a 0.1M solution of hydrochloric solution to quench the reaction. A tube was fed from the quench bottle to a secondary bottle containing saturated sodium hydroxide solution to scrub the excess CO_2.The product was extracted from the HCl solution with EtOAc. The reactions were followed by TLC (SiO_2, 1:9 MeOH:DCM, UV detection).

NOTE: The hydrochloric acid quench was changed between each experiment.

Results

A series of reaction conditions were explored to evaluate the flow rate and pressure of CO_2 required for the conversion of the Grignard to the related Carboxylic Acid.

Using the 1000ul glass microreactor at a combined flow rate of 150ul/min with gas pressure set to 0.5bar above system pressure (2 bar) full conversion to the acid was observed by TLC. The full quantitative conversion was observed up to a combined flow rate of 750ul/min after which the conversion began to drop off.

By increasing the gas pressure slightly to 0.7bar above the system pressure the conversion to the acid was observed to increase again.

These observation held true when the system pressure was increased in increments up to 12 bar if the gas pressure was maintained at 0.5bar above system pressure.

Flow Rate (ml/min)	System Pressure (bar)	Gas Pressure (bar)	Conversion (100 %)
150	2	2.5	Y
250	2	2.5	Y
500	2	2.5	Y
750	2	2.5	N
750	2	2.7	Y
500	5	5.5	Y
500	8	8.5	Y
500	10	10.5	Y
500	12	12.5	Y

***Table 1**: Conversions using an Asia 1000µl Microreactor Chip 3 Input*

Using a 4ml fluoropolymer tube reactor we repeated the experimental conditions set out above. At combined flow rates below 1000ul/min with a gas pressure maintained 0.5bar above system pressure (2 bar) a full conversion was observed.

At flow rates above the conversion dropped and we were able to see the full consumption of CO_2 in the reaction (see figure 4). By either decreasing the flow rate or again increasing the gas pressure slightly to 0.7 bar above systm pressure full conversion was observed.

Flow Rate (ml/min)	System Pressure (bar)	Gas Pressure (bar)	Conversion (100 %)
1000	2	2.5	Y
1250	2	2.5	N
1250	2	2.7	Y

***Table 2**: Conversions using an* Asia 4ml Tube Reactor Fluoropolymer

NOTE: A regulator with fine pressure adjustment is required to precisely control the gas pressure.

This figure shows the reaction limited by available CO_2 seen by the band in the centre of the reactor where no gas/liquid partition is observed.

Figure 5: *Reaction limited by available CO_2 gas.*

The two images below (figure x) show the 1000ul glass microreactor and 4ml fluoropolymer tube reactor with 1:1 ratios of gas:liquid

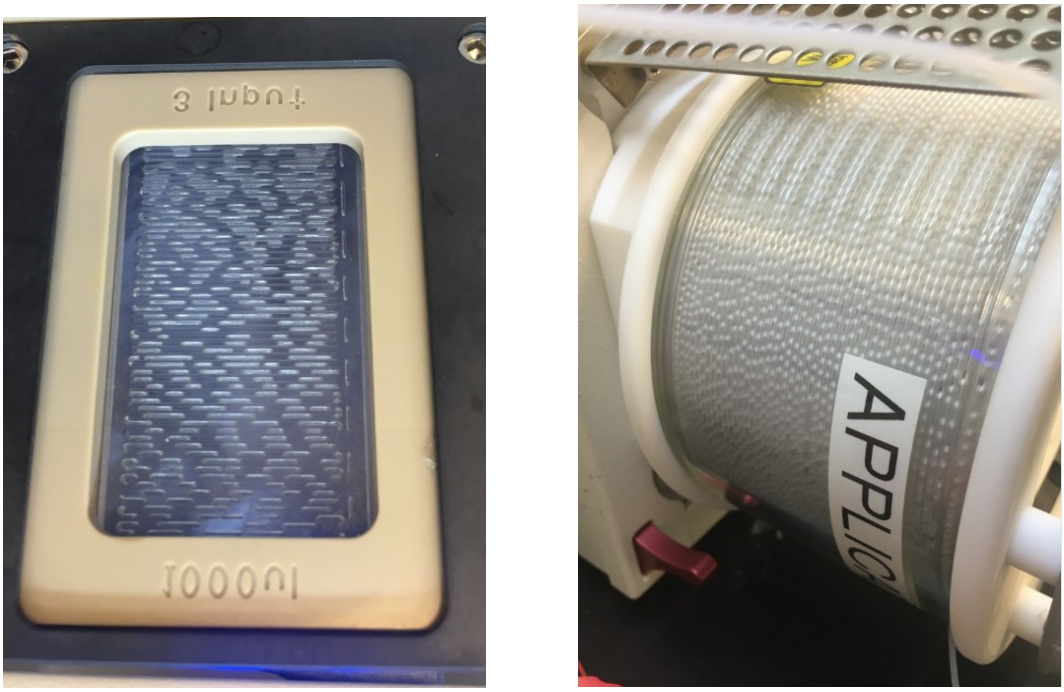


Figure 6: *1:1 Ratio of Gas:Liquid with Syrris Asia Reactors.*

Conclusion

Using the Asia Flow Chemistry System, we have successfully demonstrated an easy-to-use, safe, continuous method for the introduction of reactive gases in a liquid/gas plug-flow method under anhydrous conditions.

Appendix A: System Component List

Part No.	Part Description
2200400	Asia Pressurized Input Store
2200292	Asia Pump
2200520	Asia Reagent Injector (fitted with 5ml Sample Loops)
2200526	Asia Chip Climate Controller
2200532	Asia Pressure Controller
2100146	Asia 1000ml Microreactor Chip 3 Input
2200541	Asia 4ml Tube Reactor Fluoropolymer

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