

GAS-LIQUID MICROFLUIDIC REACTORS FOR THE OXIDATIVE HOMOCOUPLING OF PHENYLACETYLENE

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ABSTRACT

We report a new approach for performing oxidative homocoupling reactions. Specifically, a gas-liquid microfluidic reactor was developed to carry out the Glaser-Hay reaction of phenylacetylene. A range of reaction conditions were sampled to find those that produced the highest yields of 1,4-diphenylbutadiyne. Product yields of up to 100% were attained in very short residence times (7-30 min) and under standard experimental conditions when compared to conventional synthetic methods. These studies represent the first multiphase microfluidic method for the synthesis of diynes.

KEYWORDS: Microfluidics, segmented flow, gas-liquid, Glaser-Hay reaction, homocoupling

INTRODUCTION

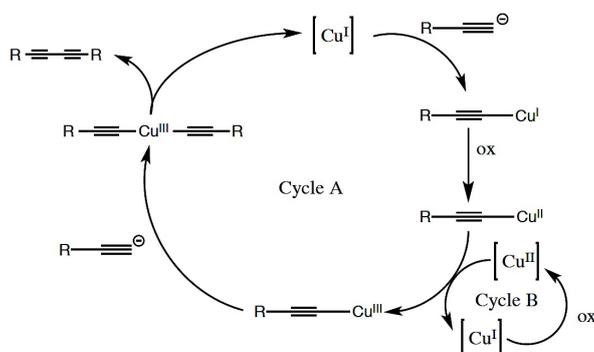
Conjugated diynes are of high practical importance since they lead to polyynes, which exhibit graphene-like properties [1]. The Glaser-Hay homocoupling reaction is the most common method used to join acetylenes to form butadiynes [2,3]. From the literature, it is observed that conventional synthetic methods show average to high yields of the produced alkynes for reaction times between 1 and 24 hours [1-6]. Petersen *et al.* suggested a continuous flow microfluidic method for the formation of 1,3-butadiynes using a gas permeable Teflon AF-2400 tube-in-tube reactor [7]. However, the use of high pressures (4-9.5 bar) and high temperatures (>100°C) require the use of high-pressure equipment and elaborate safety procedures, even when performing the reaction in a microfluidic environment.

Gas-liquid segmented flow microfluidic technology offers new opportunities for studies in oxidative homocoupling reactions. Our method involves the generation of microscale air bubbles within a liquid reaction mixture. The proposed microfluidic system has two main advantages over previous experimental formats: enhanced reagent mixing in the liquid slugs, and dosing control from the bubbles to the slugs.

THEORY

Generally, the Glaser-Hay reaction is carried out under mild conditions. The original synthesis of 1,3-diynes involves an alkyne and catalytic amounts of CuCl with a bidentate complexing ligand (TMEDA), which are dissolved in an appropriate solvent (acetone, 2-propanol) in the presence of dioxygen [3]. Many modifications and improvements have been introduced since the reaction was discovered. Most of these studies have focused on making the reaction environmentally friendly, economical and efficient. For these reasons, different organic solvents [8], hydrofluorocarbon liquids [1] and bases [8] have been examined. Solvent-free processes and synthetic procedures without the presence of ligands and bases have also been reported, however in these cases high temperatures and pressures are required [5]. Recently, Vilhelmsen *et al.* investigated the kinetics of the Glaser-Hay reaction carrying out ¹³C NMR experiments [4]. In their investigations, they found that the reaction is zero-order under standard experimental conditions. However, they observed slower kinetics due to the inhibiting influence of water on the catalyst. This was the first study reporting the effect of accumulated water from the air on the reaction yield. Scheme 1 shows the suggested mechanism for the catalyst cycles involved in the Glaser-Hay reaction.

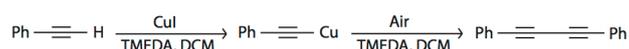
This complex system is an ideal choice for study in segmented-flow microfluidics. On the microscale, the presence of water in the precursor solutions (and also in the reaction mixture as a byproduct) shows a tremendous influence on reaction yield. After testing different reaction systems, we decided to study the formation of 1,4-diphenylbutadiyne starting from phenylacetylene and using the catalytic system CuI/TMEDA in dichloromethane.



Scheme 1: Suggested mechanism for Cu^I/Cu^{II}/Cu^{III}/Cu^I cycles [4].

EXPERIMENTAL

Scheme 2 shows the model Glaser-Hay reaction used for the synthesis of 1,4-diphenylbutadiyne. The experimental setup consists of two parts (Figure 1), a glass microfluidic chip (Micronit FC_R150.332.2_Pack) for the generation of monodisperse bubbles and perfluoroalkoxy (PFA, Ercatech) tubing for increasing the effective reaction time (0.8 μm interior diameter). CuI (30.9 mg, 0.31 mmol, ABCR) and TMEDA (0.13 ml, 0.87 mmol, ABCR) were dissolved in 25 ml of CH_2Cl_2 (Merck) to form the catalyst solution. The substrate solution was formed by dissolving phenylacetylene (0.33 ml, 3.00 mmol, AlfaAesar) in 5 ml of CH_2Cl_2 . Prior to syringe filling, 4 \AA molecular sieves were added to both solutions to remove accumulated water, which is known to suppress the catalyst activity [4]. The dehydrated substrate and catalyst solutions met at a PEEK tee. The mixed reaction stream was then inserted into the microfluidic chip together with air to create liquid slugs separated by gas bubbles (Figure 2). The generation of the bubbles could be controlled with a mass flow controller (Bronkhorst, F-200CV). Due to the plug-like shape of the formed bubbles (Figure 2), they move at the same velocity as the liquid slugs [9], therefore allowing the reaction time for each experiment to be calculated with precision. The collected samples were analyzed with a GC-FID (HP 6890, Agilent Technologies Inc., Switzerland) fitted with an autosampler and autoinjector and a 30 m (5%-phenyl)-methylpolysiloxane non-polar column (HP-5, 250 μm I.D.). The reaction yields were calculated using calibration plots of the pure reagents.



Scheme 2: Oxidative coupling of phenylacetylene to form 1,4-diphenylbutadiyne. DCM = 1,2-dichloromethane.

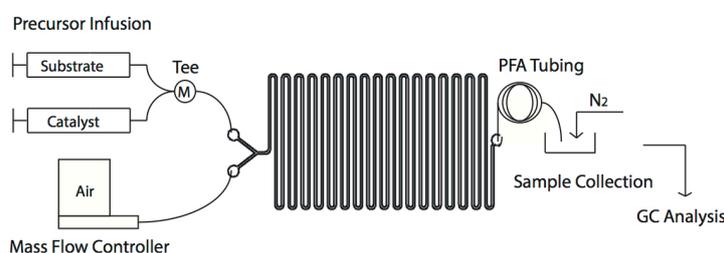


Figure 1: Schematic of the experimental setup

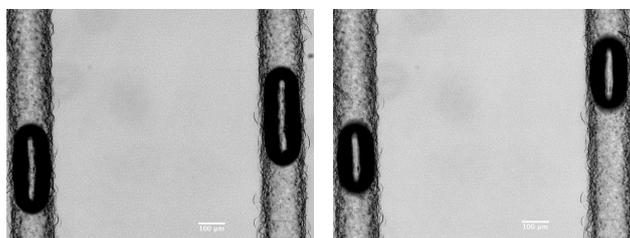


Figure 2: Images of the air plugs in the reagent mixture. By adjusting the air pressure or the precursors flow rates, different bubble sizes could be formed.

RESULTS AND DISCUSSION

Initially, the formation of 1,4-diphenylbutadiyne was performed using different solvents (2-propanol and acetonitrile), however the obtained product yields were low due to the poor solubility of the catalyst and the presence of water in the reaction mixture (Table 1). Accordingly, dichloromethane was used to improve catalyst solubility. The effects of different experimental parameters on the reaction yield were investigated in detail (Table 2). Using a 30-minute reaction time at 0.4 bar, an 100% product yield was achieved.

Table 1: CuI/TMEDA homocoupling reaction of phenylacetylene with various solvents

Entry	P (bar)	$Q_{\text{Substrate}}$ ($\mu\text{l}/\text{min}$)	Q_{Catalyst} ($\mu\text{l}/\text{min}$)	Time (min)	Yield (%)	Solvent
1	0.5	2.0	4.8	16.0	20.2	$\text{C}_3\text{H}_8\text{O}$
2	0.6	6.0	12.0	10.0	10.0	$\text{C}_3\text{H}_8\text{O}$
3	0.5	7.0	10.0	10.0	7.0	$\text{C}_2\text{H}_3\text{N}$
4	0.5	11.0	16.0	8.0	6.0	$\text{C}_2\text{H}_3\text{N}$

Table 2: The effects of different experimental parameters on the Glaser-Hay coupling of phenylacetylene in dichloromethane (reactions were carried out on a 3 mmol scale).

Entry	P (bar)	Q _{Substrate} (μl/min)	Q _{Catalyst} (μl/min)	Time (min)	Yield (%)
1	0.5	18.0	18.0	15.0	8.0
2	0.5	11.5	27.5	15.0	15.5
3	0.5	7.0	29.0	15.0	24.0
4	0.5	5.4	32.6	15.0	36.7
5	0.4	4.0	16.0	30.0	99.2
6	0.4	5.0	14.0	30.0	100.0

Moreover, it was found that catalyst/substrate molar ratios within the liquid slugs had a pronounced effect on reaction efficiency. High catalyst/substrate flow rate ratios (at constant gas pressure) lead to high product yields even for low reaction times (Figure 3). The high flow rate ratios between the catalyst solution and the substrate solution approximate the dropwise addition of the alkyne to reaction mixture, which was reported by Hay [3].

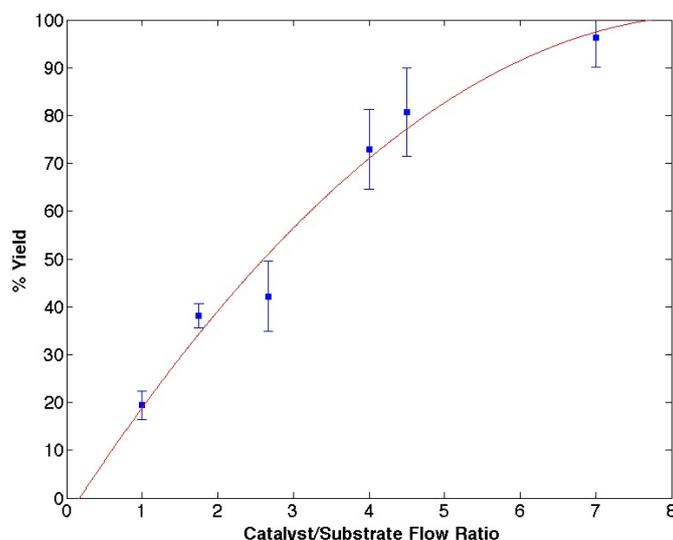


Figure 3: Percentage yield of 1,4-diphenylbutadiyne as a function of catalyst/substrate flow rate ratio (Reaction time = 7 min, $P_{air} = 0.7$ bar).

CONCLUSION

The microfluidic system used in this study is simple to fabricate, easy to use and allows a broad range of experimental conditions to be sampled within short time frames. We propose to use this multiphase system for kinetic studies of the Glaser-Hay reaction and for reactions where the intimate contact between gases and liquids is crucial.

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