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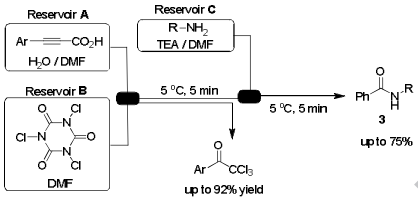

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Continuous Flow Reaction System for the Synthesis of 2,2,2-Trichloroacetophenone Derivatives and Its Application

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ABSTRACT

A continuous flow reaction system was developed for the synthesis of 2,2,2-trichloroacetophenone derivatives. When aryl propiolic acids and water were mixed with trichloroisocyanuric acid in DMF at 5 °C, the 2,2,2-trichloroacetophenone derivatives were formed within 5 min with good yields. In addition, the resulting mixture was flowed to react with amines to give the corresponding benzamide. This flow reaction system provided higher yields within shorter times than the batch reaction system.

Trichloroacetophenone moieties are found in bioactive compounds such as pesticides, herbicides, fungicides, and preservatives and have been used as building blocks in organic syntheses (Figure 1).[1] In addition, the trichloromethyl ketone group has been used as an acyl chloride surrogate in acyl substitutions.[2]

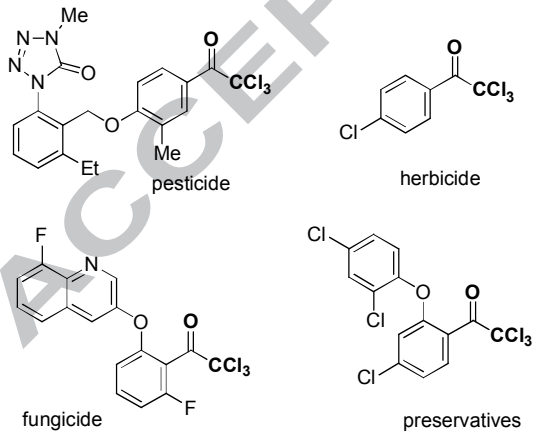

Figure 1. Bioactive compounds of trichloroacetophenone derivatives

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Although it is more stable and less sensitive to moisture compared to acyl chloride, synthetic methods for the preparation of trichloroacetophenone derivatives have not been well developed. In most cases, trichlorinated reagents such as chloroform, trichloroacetate, trichloroacetonitrile, and chloral have been used as starting materials for the synthetic process. As the most common method, the reaction with aldehydes and trichlorinated reagents provides the corresponding alcohols, and subsequent oxidation affords the desired trichloroacetophenone derivatives.[3] However, two steps are required for this synthesis. As alternative methods, related syntheses using the reactions of Grignard reagents or aryl boronic acids have been developed.[4] However, all previously developed methods have some drawbacks, as Grignard reagents are moisture-sensitive and aryl boronic acids require metal catalysts for completion of the reaction. To address these issues, we recently developed a mild synthetic method for the preparation of trichloroacetophenone derivatives via the reaction of aryl alkynoic acid and trichloroisocyanuric acid.[5] The synthesis was carried out at room temperature in the presence of water and afforded the desired products in good yields. In addition, the corresponding esters, amides, and hydrizides from the reaction of alcohols, amines, and hydrazines were easily produced. However, temperature control was required to obtain high yields of the products because the reaction with trichloroisocyanuric acid (TCCA) is exothermic. Benzoic acid derivatives were formed as by-products from the reaction of the final product with water.

The process of performing chemical reactions using a continuously flowing stream, called flow chemistry, has been developed over the past decade.[6] The significant advantages of flow chemistry have led to its application in organic synthesis

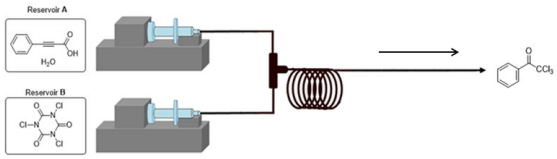
and it is a rapidly growing field of research.[7] In particular, flow chemistry technology has been successfully applied for the preparation of fine chemicals, natural products, and pharmaceutical building blocks.[8]

In a conventional batch reactor, reaction times are long and the product yields are typically low. In addition, it is difficult to scale up due to the difficulty in conducting experiments while maintaining same temperature in all regions of the batch reactor. Conversely, flow chemistry has advantages such as easy control of heat and mass transfer, controlled mixing, and high surface to reactor volume ratio.[9] When reaction conditions are optimized in a flow system, several reactors can be placed in series to produce products without scale up. In a batch reactor, it is difficult to control rapid exothermic reactions. However, the high surface to reactor volume ratio in flow systems allows for efficient heat transfer and the effective removal of heat generated from the reaction. Owing to the numerous advantages of flow chemistry, higher yields and selectivity can be obtained when compared to conventional batch reactors in organic syntheses.[10]

To optimize the conditions in flow reaction systems, two reservoirs were prepared and connected to the flow channel. Phenylpropiolic acid was dissolved in a mixture of water and CH_3CN and transferred to reservoir **A**. Trichloroisocyanuric acid was slowly added to the CH_3CN solvent and transferred to reservoir **B**. As shown in Table 1, first, we used a low concentration of TCCA in CH_3CN and allowed it to flow at 25 °C. When the mixture was flowed for 120 min, trichloroacetophenone was formed in 22% yield (entry 1). The yield of the product was similar even with a longer residence time. However, the flow clogged at 50 °C (entry 3) and to solve this issue, acoustic radiation was introduced using a sonicator (entry 6 and 7). Another potential solution was to use three-fold higher TCCA concentration than phenylpropiolic acid concentration (entries 4 and 5). With higher concentrations, a 72% product yield was obtained at 60 °C (entry 4), but the yield decreased to 54% at 80 °C (entry 5). With much higher concentration, the desired product was formed in 71% yield when the residence time was 20 min (entry 6). Clogging issues were apparent when the reaction was flowed for 40 min (entry 7). As an alternative method to solve the clogging issue, we used DMF as the reaction solvent. The concentration of the reactant was kept 0.3M and the reaction was flowed without a back-pressure regulator. This system provided the product in 71% yield at 25 °C and in 59% yield at 40 °C (entries 8 and 9). When the reaction temperature was decreased to 10 °C and 5 °C, the product yield was increased to 79% and 84%, respectively (entries 10 and 11). When the residence time was reduced to 10 and 5 min, the product yields were 86% and 91%, respectively (entries 12 and 13). However, the product yield decreased to 69% at 0 °C (entry 14). It should be noted that this flow reaction system provided the desired product in better yields than the corresponding batch reaction system. No benzoic acid by-products were found in the reaction mixture and trichloroacetophenone was generated in 5 min

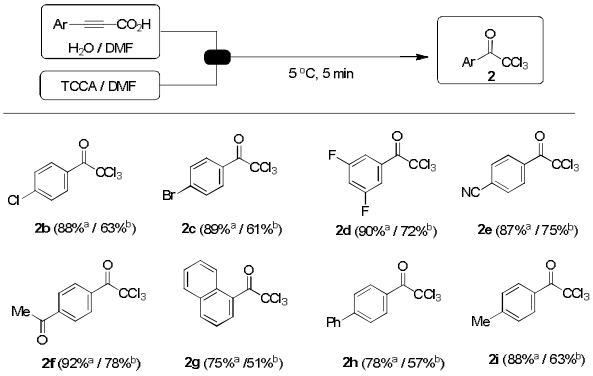
With the optimized flow conditions, the resultant substituted aryl propiolic acids were evaluated, as shown in Scheme 1. Halo-substituted aryl propiolic acids **1b**, **1c**, and **1d** gave corresponding 2,2,2-trichloroacetophenone derivatives **2b**, **2c**, and **2d** in 88%, 89%, and 90% yields, respectively. Aryl propiolic acids containing electron-withdrawing groups such as cyano and ketone groups provided the desired product in good yields. 1-Naphthylpropiolic acid and (1,1'-biphenyl)-4-ylpropiolic acid afforded the corresponding 2,2,2-trichloroacetophenone derivatives **2g** and **2h** in 75% and 78% yields, respectively. *p*-Tolylpropiolic acid gave **2l** in 88% yield. This flow system provided higher yields than the batch system in all cases and the desired products were formed in 5 min

Table 1. Optimization of the flow reaction system conditions for the synthesis of 2,2,2-trichloroacetophenone



Entry	Solvent	Condition[a]	BPR[b]	Temp (°C)	Residence Time (min)	Yield (%)[c]
1	CH_3CN	**I**	X	25	120	22
2	CH_3CN	**I**	X	25	240	25
3	CH_3CN	**I**	X	50	120	-
4	CH_3CN	**II**	X	60	20	72
5	CH_3CN	**II**	O	80	20	53
6	CH_3CN	**III**	O	70	20	71
7	CH_3CN	**III**	O	70	40	-
8	DMF	**IV**	X	25	20	71
9	DMF	**IV**	X	40	20	59
10	DMF	**IV**	X	10	20	79
11	DMF	**IV**	X	5	20	84
12	DMF	**IV**	X	5	10	86
13	DMF	**IV**	X	5	5	91(90)[d]
14	DMF	**IV**	X	0	5	69

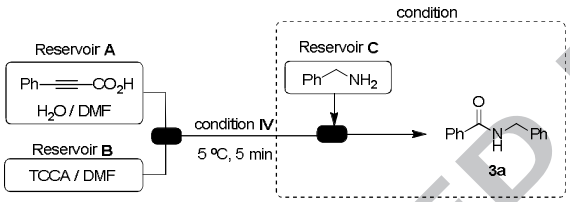
[a]Condition **I**: Reservoir **A** = **1a** (4.25 mmol) / H_2O (68.0 mmol) / CH_3CN (15.0 mL), Reservoir **B** = TCCA (4.25 mmol) / CH_3CN (15.0 mL), Condition **II**: Reservoir **A** = **1a** (4.25 mmol) / H_2O (68.0 mmol) / CH_3CN (15.0 mL), Reservoir **B** = TCCA (12.75 mmol) / CH_3CN (15.0 mL), Condition **III**: Reservoir **A** = **1a** (8.50 mmol) / H_2O (136.0 mmol) / CH_3CN (15.0 mL), Reservoir **B** = TCCA (12.75 mmol) / CH_3CN (15.0 mL). The reaction mixture was treated with a sonicator. Condition **IV**: Reservoir **A** = **1a** (4.25 mmol) / H_2O (68.0 mmol) / DMF (15.0 mL), Reservoir **B** = TCCA (4.25 mmol) / DMF (15.0 mL) [b]BPR = back pressure regulator, X = no BPR, O = with BPR. [c]Determined by gas chromatography with an internal standard. [d]Isolated yield.



Scheme 1. Synthesis of 2,2,2-trichloroacetophenone derivatives using a flow reaction system. Reaction condition: Reservoir **A** = **1** (4.25 mmol) / H_2O (68.0 mmol) / DMF (15.0 mL), Reservoir **B** = TCCA (4.25 mmol) / CH_3CN (15.0 mL) [a]Isolated yield. [b]Yield from the batch reaction. Reaction condition : **1** (2.0 mmol), TCCA (2.2 mmol) and H_2O (32.0 mmol), were reacted in CH_3CN (5.0 mL) at 25 °C for 12 h.

Trichloroacetophenone was also used as an acyl chloride surrogate in a batch reaction system. In a previous study, we reported that the reaction of amine and trichloroacetophenone provided the corresponding amide. In addition, we showed that the desired amide could be obtained through sequential reactions of decarboxylative chlorination and acyl substitution. Based on the previous batch reaction results, we attempted to develop a flow reaction system for the synthesis of benzamides from phenylpropiolic acid. Benzylamine was chosen as the amine for the reaction with 2,2,2,-trichloroacetophenone. We examined a variety of parameters to optimize the conditions for the continuous acyl substitution reaction. The solution of benzylamine and additives was added to the mixture of the final product provided from the flow reaction of phenylpropiolic acid and TCCA. The results of the optimization experiments are summarized in Table 2. First, we evaluated additives such as 4-dimethylaminopyridine (DMAP), triethylamine (TEA), and *N,N,N',N',N''*-pentamethyldiethylenetriamine (PMDETA) at 5 °C under 5 min flow conditions. When DMAP and PMDETA were used, *N*-benzylbenzamide was formed in 41% and 52% yields, respectively (entries 1 and 3). The addition of TEA afforded the desired product in 75% yield (entry 2), but increasing the reaction temperature did not provide higher yields than the reaction at 5 °C (entries 4 and 5). CH_3CN and THF as solvents did not give satisfactory results (entries 6 and 7).

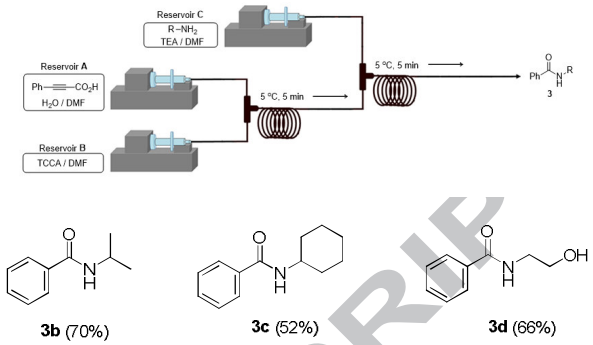
Table 2. Optimization of the continuous flow reaction system for the synthesis of benzamides.



Entry	Solvent	Additive	Temp	Time	Yield (%)
1	DMF	DMAP	5	5	41
2	DMF	TEA	5	5	75
3	DMF	PMDETA	5	5	52
4	DMF	PMDETA	30	5	46
5	DMF	PMDETA	50	5	44
6	CH_3CN	PMDETA	5	5	-
7	THF	PMDETA	5	5	-

[a]Condition: Reservoir **A** = **1a** (4.25 mmol) / H_2O (68.0 mmol) / DMF (15.0 mL), Reservoir **B** = TCCA (4.25 mmol) / DMF (15.0 mL). Reservoir **C** = benzylamine (8.5 mmol), additive (0.85 mmol). [b]Isolated yield based on phenylpropiolic acid.

After optimization of the continuous flow system, we evaluated it for the synthesis of amides from phenylpropiolic acid. As shown in Scheme 2, the desired benzamides were formed in good yields. When the solution of isobutylamine was connected to a second flow reactor and run at 5 °C for 5 min, *N*-isobutylbenzamide was formed in 75% yield. The reaction with cyclohexylamine provided *N*-cyclohexylbenzamide (**3c**) in 52% yield. When 2-aminoethanol was used in the second flow reactor, the desired product **3d** was formed in 66% yield.



Scheme 2. Continuous flow reaction for the synthesis of amides

In conclusion, we developed a continuous flow reaction system for the preparation of 2,2,2-trichloroacetophenone derivatives from the reaction of aryl propiolic acids and trichloroisocyanuric acid. The yields from the flow reaction system are generally higher than those obtained from the batch reaction. Benzoic acid derivatives are commonly formed as by-products formed from the side reaction of 2,2,2-trichloroacetophenone with leftover water. However, no benzoic acid derivatives formed in the flow reaction system because the reaction was faster and occurred at lower temperatures. The mixture formed in the first step was continuously connected to an amine solution to provide the desired benzamides in good yields. These two-step flow reaction systems provided the benzamide products in 10 min from phenylpropiolic acid. All the reactions yields in this flow reaction system were higher than those in the corresponding batch reactions.

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Highlights

Flow system for the decarboxylative trichlorination of alkynyl carboxylic acid

Synthesis of 2,2,2-trichloroacetophenone derivatives

Continuous flow reaction for the synthesis of amide from alkynyl carboxylic acid