Tetrahedron Letters 67 (2021) 152876

Contents lists available at ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

1,3-Dibromo-5,5-dimethylhydantoin (DBH)/DMSO mediated oxidative difunctionalization of styrenes: Microfluidic synthesis of pentafluorophenoxy ketone

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ARTICLE INFO

Article history:
Received 11 September 2020
Revised 21 January 2021
Accepted 25 January 2021
Available online 4 February 2021

Keywords:
Continuous flow system
Metal-free
DBH/DMSO
Pentafluorophenoxy ketone

ABSTRACT

A practical and mild synthesis of pentafluorophenoxy ketone in a continuous flow microfluidic reactor has been developed through 1,3-Dibromo-5,5-dimethylhydantoin (DBH)/DMSO mediated oxidative coupling of styrenes with pentafluorophenol. Moreover, a series of pentafluorophenoxy ketone products were provided in moderate to good yields under metal-free conditions. A magnifying continuous flow system was erected to verify the appliance of this method.

The unique electronic properties of fluorine increase the lipophilicity, bioavailability and metabolic stability of organic molecules [1]. Adding a fluorine-containing group to an organic molecule has a profound influence on its chemical, physical and biological properties [2]. Fluorine-containing group modification of the target molecules has become a important practice at every stage of preclinical drugs development, and lots of candidates with fluorine-containing groups have been developed [3]. Thus, introducing fluorine-containing groups into some organic compounds draws continuous attention form chemists around the world [4]. Actually, it is a common method to insert fluorine-containing groups through the difunctionalization of alkenes [5]. Guo's group discovered a process of synthesis of fluorophenoxy substituted *N*-heterocycles with polyfluoro-alcohols [6]. A method for hydroxytrifluoromethylation of alkenes with Langlois reagent and DMSO has been reported by Liu's group [7].

Alkenes are one of the most readily available synthesis units which its difunctionalization provides the most attractive solution for the synthesis of various organic compounds [8]. A large number of metal-catalyzed alkenes difunctionalizations have been reported in recent years, such as oxo-nitrogenation, oxo-hydroxylation and oxo-amidation [9]. Despite some progress have been made, the high cost, toxicity and environmental impact of using metal catalysts have further limited its application in the development of pharmaceutical products, not to mention the selective difunctionalization of alkenes is still a challenge [10]. Thus, it's of great significance to develop a metal-free difunctionalization method of alkenes. Recently, highly region-selective difunctionalization of alkenes could be achieved via X_2/HX-DMSO mediated oxidative halogenations have been reported [11]. But the participation of halogen has some environmental problems, which limited its industrial application. Therefore, construction of mild and efficient reagent substitutes was highly demanded. 1,3-Dibromo-5,5-dimethylhydantoin (DBH) is widely used as an industrial anhydrous bleaching and sterilizing agent which also plays an important role in bromination of alkenes in chemical synthesis [12].

Recently, micro-reaction technology has been developing rapidly in green chemistry [13]. Microfluidic reactors have thinner channels with dimensions of tens to hundreds of micrometers than the traditional chemical batch reactors, so that the microfluidic reactors can make the reaction more efficient due to its highly efficient mixing and temperature control [14]. The conventional synthesis of phenacyl bromides intermediates required up to 12 h to react, while the microreactor consumed only a few minutes

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https://doi.org/10.1016/j.tetlet.2021.152876
0040-4039/

of residence time and continuously collected products, which could be easily operated and effectively applied to industrial amplification [15]. Herein, we reported a method for synthesizing pentafluorophenoxy ketone via DBH/DMSO mediated oxidative coupling of pentafluorophenol with alkenes at room temperature in continuous flow reactor. As shown in Fig.1. This continuous flow reactor system consists of two syringe pumps, one *T*-piece micromixers and one microreactors. The volume of the syringe and microreactors are 10 mL and 1.96 mL. The molar ratio and the reaction time are controlled by changing the flow rate of the syringe. The temperature is controlled by an oil bath.

In our initial studies, styrene **1a** and Pentafluorophenol **2a** were chosen as a model substrate for application in the microfluidic reactor. The product **3a** could be formed under the system of DBH/DMSO. Encouraged by this result, the reaction conditions have been explored and the results were summarized in Table 1. Initially, different bases were screened, including DBU, Et_3N, DMAP, which showed that Et_3N was found to be the favourable choice (Table 1, entries 1–3). Then the DBH (0.5 equiv.) and the Pentafluorophenol **2a** (1 equiv.) were exhibited the better effect with 81% yield of pentafluorophenoxy ketone **3a** (Table 1, entry 4). Furthermore, the temperature was also tested. When the reaction temperature was raised to 40 ℃ and 60 ℃, the yields of **3a** were decreased (Table 1, entries 8–9). In order to improve the yield of the product **3a**, the residence time in the reactor was screened. But the yield of **3a** was reduced regardless of decreasing or improving the flow rate. (Table 1, entries 10–11). The yield was slightly decreased with the extension of the reaction time due to a smaller average speed in a microfluidic reactor and leads to weaker mass transfer in the continuous flow system.

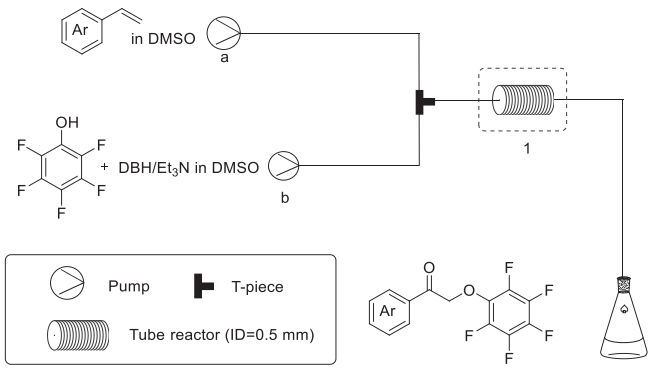
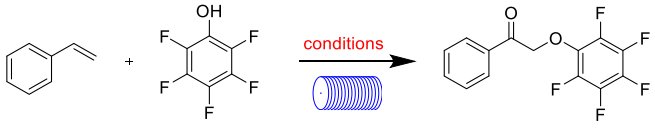


Fig. 1. A continuous flow reactor system.

Optimizations of reaction condition for the microfluidic synthesis of pentafluorophenoxy ketone from styrenes and pentafluorophenol have been obtained. Then the optimizations in batch were also screened to compare with microfluidic reactor (supporting information). The best yield of **3a** reached to 64% in batch (Table 1, entry 12), which was weaker than that in microfluidic reactor. And the reaction time prolonged to 12 h in batch, which was much longer than 10 min. Comparative results indicated that the microfluidic reactor could enhance the reaction efficiency by providing efficient mixing between the reactants, which was weaker in batch.

Having established the optimal reaction conditions in hand, we investigated the substrate scope of this transformation. As shown in Table 2, a variety of styrene derivatives including both electron-donating groups (Me, MeO, AcO, *t*-Bu, Ph) and halogenated groups (F, Cl, Br, CF_3) were chosen to certificate the general applicability of the current procedure, and all substrates reacted successfully for the synthesis of the corresponding products in good yields (Table 2. 3**b**-3**q**). Generally, the positions of substitution patterns (para-, meta-, and ortho-) have no apparent influence for this reaction (Table 2, 3**b**-3**d**, 3**i**-3**j**, 3**k**-3**m**, 3**n**-3**o**). It is noteworthy that the yield (3**b**-3**h**) of the substrate containing electron-donating groups is similar to electron-withdrawing groups (3**i**-3**p**). However, the strong electron-withdrawing groups (NO_2) substituted styrene failed to gain product (Table 2, 3**r**). In addition, heteroarenes including indene and 2-Vinylnaphthalene were also applicable for these conditions. The corresponding products **3s** and **3t** were obtained in 52% and 61% yield (Table 2, 3s, 3t). But the reactions both failed when the styrene was replaced by aliphatic alkenes or α, β-unsaturated carbonyl. (Table 2, 3u, 3v).

Table 1
Optimization of reaction conditions in continuous-flow reactor.[a,b]

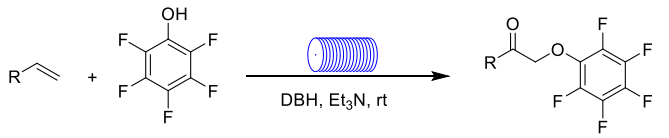


1a **2a** **3a**

Entry	base	DBH (eq)	2a (eq)	T (℃)	R_T (min)	Yield[b] (%)
1	DBU	1	1	rt	10	33
2	Et_3N	1	1	rt	10	63
3	DMAP	1	1	rt	10	20
4	**Et_3N**	**0.5**	**1**	**rt**	**10**	**81**
5	Et_3N	1.5	1	rt	10	42
6	Et_3N	0.5	0.5	rt	10	35
7	Et_3N	0.5	2	rt	10	65
8	Et_3N	0.5	1	40	10	60
9	Et_3N	0.5	1	60	10	46
10c	Et_3N	0.5	1	rt	5	51
11[d]	Et_3N	0.5	1	rt	15	63
12e	Et_3N	0.5	1	rt	–	64

[a] Reaction conditions: Solution A: 1.5 mmol 1a in 5 mL DMSO, flow rate 0.098 mL/min; Solution B: 0.75 mmol DBH, 0.75 mmol Et3N and 1.5 mmol 2a in 5 mL DMSO, flow rate 0.098 mL/min, unless otherwise noted.
[b] Isolated yields.
[c] Solution A: 3 mmol 1a in 5 mL DMSO, flow rate 0.196 mL/min; Solution B: 1.5 mmol DBH, 1.5 mmol Et3N and 3 mmol 2a in 5 mL DMSO, flow rate 0.196 mL/min.
[d] Solution A: 0.75 mmol 1a in 5 mL DMSO, flow rate 0.049 mL/min; Solution B: 0.38 mmol DBH, 0.38 mmol Et3N and 1.5 mmol 2a in 5 mL DMSO, flow rate 0.098 mL/min.
[e] The reaction is in a batch instead of a continuous-flow reactor.

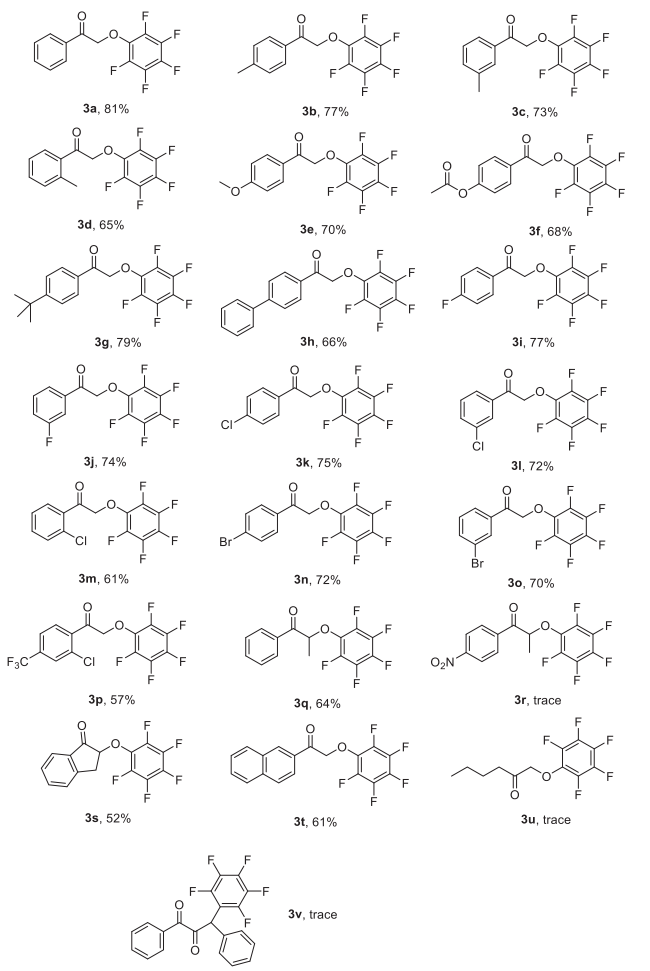
Table 2
Substrate scope of styrenes for the synthesis of 3.[a,b]



1 2a 3

[a]Reaction conditions: Solution A: 1.5 mmol 1 in 5 mL DMSO, flow rate 0.098 mL/min; Solution B: 0.75 mmol DBH, 0.75 mmol Et3N and 1.5 mmol 2a in 5 mL DMSO, flow rate 0.098 mL/min; unless otherwise noted.
[b]Isolated yields.

Table 3
Substrate scope of styrenes for the synthesis of **5a.**[a,b]



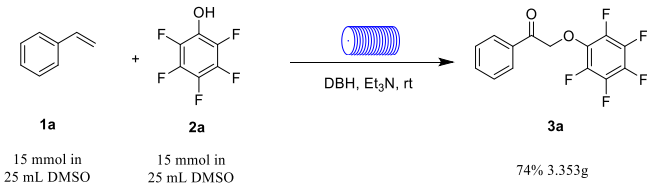
[a]Reaction conditions: Solution A: 1.5 mmol 1 in 5 mL DMSO, flow rate 0.098 mL/min; Solution B: 0.75 mmol DBH, 0.75 mmol Et3N and 1.5 mmol 2a in 5 mL DMSO, flow rate 0.098 mL/min; unless otherwise noted.
[b]Isolated yields.

Two-step flow system were designed due to failed attempts to expand the substrate range with variety of phenols (Table 3). Compared with one-step continuous flow system, the base was replaced by Na_2CO_3 after the phenacyl bromides has been generated (see Table 2 in the Supporting Information), and the solution has been changed to DMSO/H_2O (v/v = 4:1) to improve the solubility of Na_2CO_3, substituents attached on the phenols showed excellent compatibility, affording the corresponding products in 54 to 68% (Table 3, 5a-5c). In addition, trifluoroethanol can also process the corresponding product in yield of 53% (Table 3, 5d). Furthermore, pentafluorophenol was also tested in this two-step continuous flow system, and 73% yield of product **3a** was obtained, which was lower than in one-step system. This result showed that the newly generated intermediate phenacyl bromides reacted immediately to improve the yield of product **3a** in one-step continuous flow system.

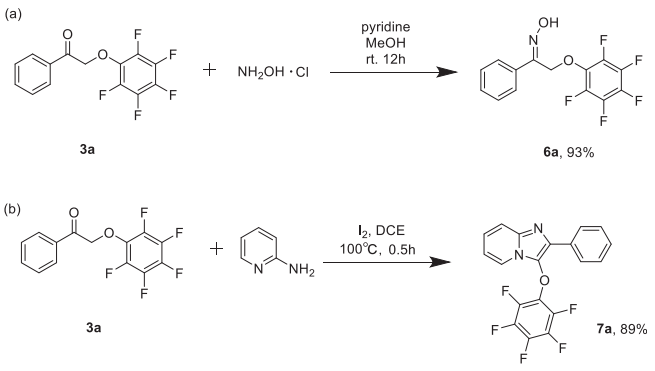
To explore the practical application of this method, a 15 mmol scale-up continuous flow reaction was set up (Scheme 1). The reaction of alkenes **1a** and pentafluorophenol **2a** performed well to afford the product **3a** in 74% yield, which could verify the high potential of this process in industrial application. In addition, the derivatization of product **3a** was conducted (Scheme 2). The product **3a** was α-oximated to generate product **6a** in the existence of hydroxylamine hydrochloride and pyridine. 3-pentafluorophenoxy imidazo heterocycles **7a** was synthesized by catalytic oxidative cyclization of 2-Amino-azaarenes with pentafluorophenoxy ketone.

In order to explore the reaction mechanism, several control experiments were investigated (Scheme 3). When different gas atmospheres (N_2, air, O_2) were tested under optimal reaction conditions in batch, the yield of product **3a** was good (Supporting Information, Table SI, entries 20–21), suggesting that O_2 was unnecessary in the reaction pathway. It was noteworthy that phenacyl bromides as the point intermediates of this method was proven by the control experiment (Scheme 3a, b).

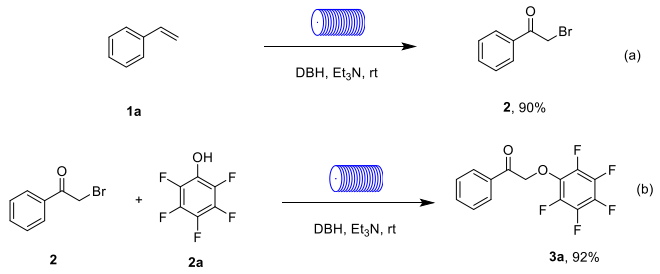
Based on the above findings and previous reports [16], a plausible mechanism for this oxidative coupling reaction is depicted in Scheme 4. The reaction pathway includes the DBH mediated synthesis of a bromonium ion **A** followed by regioselective ring opening under the effect of DMSO to give the intermediate **B**, which eliminates Me_2S to form 2-bromoacetophenone **C**. 2-bromoacetophenone, upon on Et_3N mediated nucleophilic displacement with pentafluorophenol, gives the pentafluoro-phenoxy ketone (Path 1). 2-bromoacetophenone **C** can also be reacted in a nucleophilic substitution reaction with sodium phenolate **D** to generate 2-phenoxyacetophenone **5a** (Path 2).



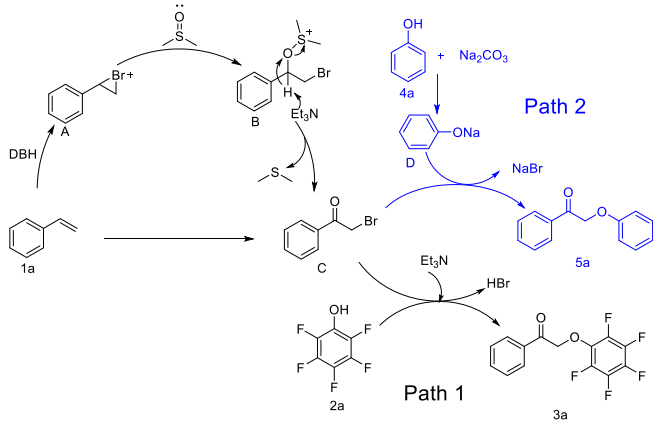
Scheme 1. A Scale-up Continuous Flow reaction.



Scheme 2. Derivatization of product 3a.



Scheme 3. Control experiments.



Scheme 4. Plausible mechanism.

In conclusion, we have developed a green and practical continuous flow synthetic method to produce pentafluorophenoxy ketone from styrenes and pentafluorophenol under DBH/DMSO system. This strategy has the advantages of its readily available raw materials, mild reaction conditions (rt), high regional selectivity and exceptional functional group compatibility. And the good yields of pentafluorophenoxy ketone products and less reaction time were achieved with continuous flow system. Finally, the process was successfully amplified, which verified its potential industrial prospects.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgments

The research was supported by the National Key Research and Development Program of China (2016YFB0301501), the National Science Foundation of China (Grant No. 21776130 & 21878145), the Jiangsu Synergetic Innovation Center for Advanced Bio-Manufacture (No. X1821 and X1802) and Postgraduate Research & Practice Innovation Program of Jiangsu Province.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.tetlet.2021.152876.

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