

Spurring Radical Reactions of Organic Halides with Tin Hydride and TTMSS Using Microreactors

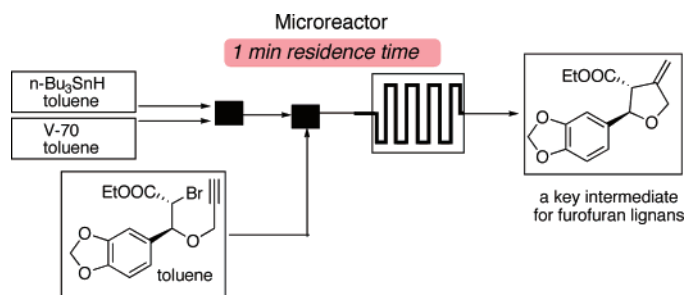
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ABSTRACT



Tributyltin hydride-mediated radical reactions of organic halides were successfully carried out in a continuous flow system using a microreactor. The reactions proceeded within a very short period of time, coupled with quickly decomposing radical initiators such as V-65 and V-70. The continuous flow reaction system was applied to gram scale synthesis of a key intermediate for furofuran lignans.

The recent evolution of microreactor technology has presented a fine opportunity for synthetic chemists to use this precisely sophisticated reaction apparatus in place of the venerable glassware batch flasks.^{1,2} We previously reported that Pd-catalyzed cross-coupling reactions such as the Sonogashira reaction,³ the Mizoroki–Heck reaction,⁴ and the carbonylative Sonogashira reaction,⁵ in which ionic liquids were used as the reaction media, could be successfully carried out using a microreactor in a continuous flow system. We

also reported on the effective execution of a [2+2]-type photoinduced cycloaddition reaction⁶ and a Barton reaction, using a glass-made microreactor in combination with a compact photoirradiation system using a black light.⁷

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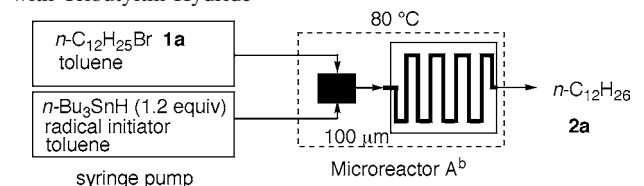
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Radical reactions are among the most fundamental in organic synthesis,⁸ and the recent progress is largely due to the use of efficient radical chain mediators such as tributyltin hydride and the related group 14 reagents.⁹ In this paper we report that typical radical chain reactions, which use tributyltin hydride and tris(trimethylsilyl)silane (TTMSS), can be successfully carried out using microreactors in a continuous flow system.¹⁰ Interestingly, we found that the reactions using tin hydride and quickly decomposing radical initiators proceed within a very short period of time, in comparison with a conventional batch system.

As a model reaction, we carried out a standard radical reduction of organic halides, using tributyltin hydride as a radical mediator. For this reaction, we used a CPC CYTOS Lab System-M equipped with a mixer having a 100 μm channel width and residence time unit with 4.5 mL inner volume (Microreactor A). The results are summarized in Table 1. When a toluene solution of 1-bromododecane (**1a**)

Table 1. Microflow Radical Reaction of 1-Bromododecane with Tributyltin Hydride^a



entry	radical initiator	concn, M	residence time, min	yield of 2a (1a), ^c %
1	AIBN, 10 mol %	0.05	8.5	96% (4%)
2	AIBN, 10 mol %	0.05	1.0	74% (25%)
3	V-65, 10 mol %	0.05	1.0	98% (2%)
4	V-65, 5 mol %	0.05	1.0	94% (4%)
5	V-65, 2 mol %	0.05	1.0	92% (8%)
6	V-70, 2 mol %	0.05	1.0	98% (trace)

^a Flow rate: 0.27 mL/min each for entry 1 and 2.3 mL/min each for entries 2–6. For details, see the Supporting Information. ^b CYTOS Lab System-M (micromixer: 100 μm channel width; residence time unit: 4.5 mL inner volume). ^c GC yield with *n*-decane as an internal standard.

was mixed with a toluene solution of tributyltin hydride (1.2 equiv) and AIBN (10 mol %) ($[\text{RBr}] = 0.05 \text{ M}$, on mixing) at 80 °C with a residence time of 8.5 min (flow rate: 0.27 mL/min), the reaction was almost complete, and a 96% yield of *n*-dodecane (**2a**), the expected reduced product, was obtained (entry 1). When the radical reaction of **1a** with tributyltin hydride and AIBN was carried out using a shortened residence time, such as 1 min, the reaction resulted in a 74% yield of **2a** with the recovery of 25% of **1a** (entry

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2). Conventional wisdom dictated that the decomposition timing of AIBN would prevent achievement of such a short reaction time. This working hypothesis led us to change the radical initiator to V-65, which decomposes more rapidly than AIBN (Figure 1). The change of the radical initiator to

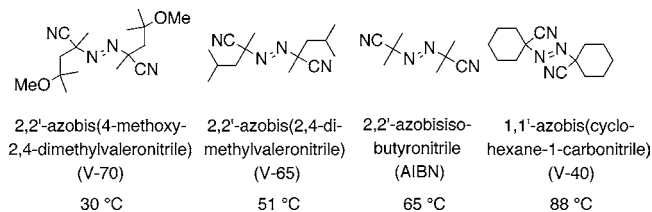


Figure 1. Ten hours half-life decomposition temperature.¹²

V-65 (10 mol %) worked quite well, and as a result, we achieved a 98% yield with a 1 min residence time (entry 3). Using a smaller amount of V-65 (2 mol %), **2a** was obtained in 92% yield along with 8% unreacted **1a** (entry 5). Subsequently, we found that the use of 2 mol % of V-70,¹¹ which decomposes more rapidly than V-65, achieved a complete reaction (entry 6). For comparison, we checked the batch reaction; the reaction of a 5 mL solution of **1a** (0.05 M) with 2 mol % of V-65 using a test tube (15 mm i.d.) for 1 min resulted in a lower conversion (**2a**: 69%; **1a**: 31%). We assume that higher thermal efficiency inherent to tiny reaction channels would ensure efficient reaction in the microreactors.

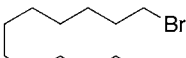
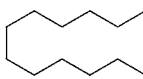
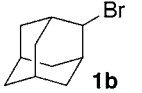

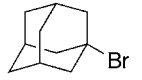
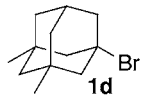

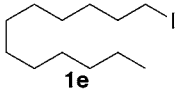
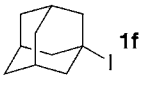
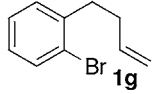
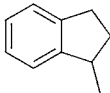
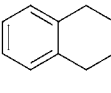
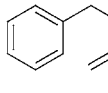
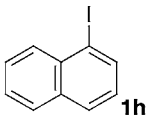
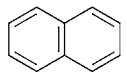
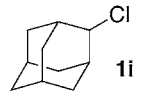
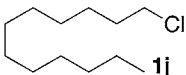
To study the generality of the high-speed radical reaction using Microreactor A, we examined the reduction of a variety of organic bromides and iodides (Table 2). In most cases, V-70 was used for radical reactions of organic bromides and iodides, which were complete in 1 min. Aryl radical cyclization starting from **1g** also worked satisfactorily (entry 10). We also tested two other types of microreactors: a microreactor system with a larger volume residence time unit (Microreactor B: CYTOS Lab System-L, 100 μm channel width, inner volume 15 mL) and a microreactor system with a different micromixer (Microreactor C: MiChS- α mixer with 200 μm channel size connected with a stainless-steel tube reactor (1000 μm i.d. \times 1 m)), both of which worked well (entries 2, 5, 6, and 7).

Encouraged by successful execution of typical radical reduction and cyclization of organic bromides and iodides using microreactors, we then studied the radical reaction of alkyl chlorides **1i** and **1j**, which are known to be less efficient

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Table 2. Radical Reaction of RI, RBr, and RCl by Bu₃SnH under Microflow Conditions^a

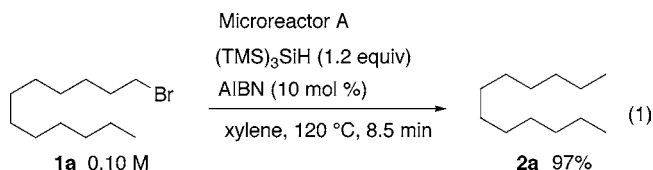
entry	RX 1	microreactor ^b	initiator	conditions	R-H 2	yield, % ^c	
1		A	V-70, 2 mol %	0.05 M, 80 °C, 1 min		98%	
2	1a	C	V-70, 2 mol %	0.05 M, 80 °C, 1 min	2a	97%	
3		A	V-70, 2 mol %	0.05 M, 80 °C, 1 min		98%	
4		A	V-70, 2 mol %	0.05 M, 80 °C, 1 min	2b	97%	
5	1c	B	AIBN, 10 mol %	0.05 M, 80 °C, 8.5 min	2b	92%	
6		B	AIBN, 10 mol %	0.05 M, 80 °C, 8.5 min		92%	
7	1d	C	V-70, 2 mol %	0.05 M, 80 °C, 1 min	2c	99%	
8		A	V-70, 2 mol %	0.05 M, 80 °C, 1 min	2a	94%	
9		A	V-70, 2 mol %	0.05 M, 80 °C, 1 min	2b	97%	
10		A	V-70, 5 mol %	0.05 M, 80 °C, 1 min	 2g 86%	 2g' 5%	 2g'' 8%
11		A	AIBN, 10 mol %	0.2 M, 130 °C, 1 min	 2h	92%	
12 ^d		A	AIBN 10 mol %	0.05 M, 120 °C, 15 min	2b	55% ^e	
13 ^d	1i	A	V-40 10 mol %	0.4 M, 130 °C, 15 min	2b	95%	
14 ^d		A	V-40 10 mol %	0.4 M, 130 °C, 15 min	2a	95%	

^a Conditions: [RX] = 0.05 or 0.2 or 0.4 M in toluene, Bu₃SnH (1.2 equiv). ^b Microreactor A: CYTOS Lab System-M with CYTOS-M mixer with 100 μm channel width and residence time unit (inner volume 4.5 mL). Microreactor B: CYTOS Lab System-L with CYTOS mixer with 100 μm channel width and residence time unit (inner volume 15 mL). Microreactor C: MiChS α mixer with 200 μm channel width and tubular reactor (1000 μm i.d. × 1 m). ^c GC yield. ^d Xylenes were used as the solvent. ^e **1i**: 44%.

due to a stronger carbon–chlorine bond than carbon–bromine and iodine bonds.¹³ In this case, the reaction using AIBN was not satisfactory even at elevated temperature (120 °C) with extended reaction time (15 min) (entry 12). However, we were again able to solve the problem by simply changing the radical initiator to V-40 (Figure 1), which decomposes more slowly than AIBN (entries 13 and 14).

We also examined a microflow reduction of **1a** using TTMSS ((TMS)₃SiH)¹⁴ instead of tributyltin hydride, to examine how this slower radical mediator would work in the microflow system. Exposure of the reaction mixture to

the reaction conditions (V-65, 120 °C, 5 min) resulted in an 80% yield of **2a** with a significant amount of unreacted **1a**. In this case, however, the use of AIBN worked well, with a slightly extended reaction time of 8.5 min (97% yield) (eq 1).

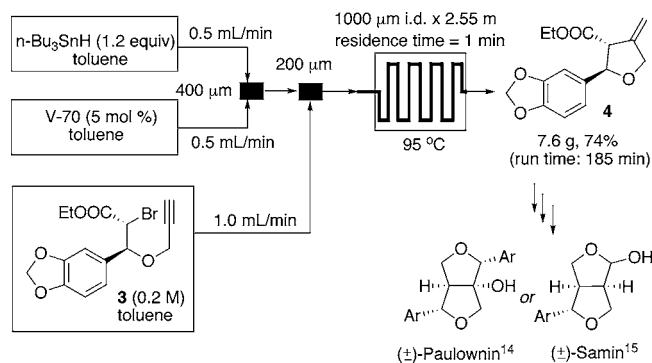


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Using Microreactor C, we examined gram-order synthesis of a tetrahydrofuran derivative **4**, which is a key intermediate

for the synthesis of naturally occurring furofuran lignans, e.g., paulownin¹⁵ and samin¹⁶ (Scheme 1). Since the total

Scheme 1. Gram Scale Synthesis of a Tetrahydrofuran Derivative **4**



operation time for multigram-scale synthesis of **4** is relatively long, we adopted a dual micromixing system to avoid undesirable decomposition of Bu_3SnH during this time frame. The radical cyclization of unsaturated α -bromo ester **3** was complete in 1 min reaction time. To achieve a

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multigram quantity, the microflow system was run for a total of 185 min, which gave 7.6 g of **4** (74% yield) after chromatographic separation.¹⁷

In conclusion, we have shown that typical tin hydride and TTMSS-mediated radical reactions of organic halides can be successfully carried out using a continuous flow reaction system equipped with microreactors. The superior thermal efficiency inherent to tiny reaction channels allowed for the rapid execution of radical reactions, when coupled with the judicious choice of the radical initiator. We have also demonstrated that the continuous microflow system has good potential for preparative scale synthesis with an example of a key intermediate for furofuran lignans.

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Supporting Information Available: Experimental procedures, ¹H and ¹³C NMR spectral data of compound **4**, and photographs of microreaction devices. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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(17) See the Supporting Information for experimental details and spectral data of **4**.