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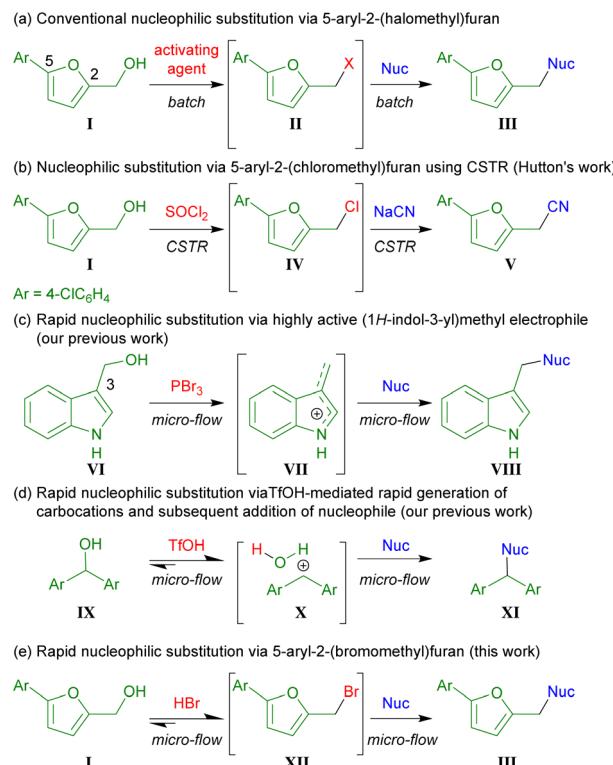
The furan ring has been recognized as an important structure,¹ ranking as the 29th most frequently used among the 378 ring systems found in marketed drugs,² and is frequently found in bioactive natural products.³ In particular, 2,5-disubstituted furans are frequently found in pharmaceuticals.⁴ Heteroatom alkylations and arylations have been reported to be the most widely used organic transformations in the pharmaceutical field over the past four decades.⁵ Therefore, the development of heteroatom alkylations for the synthesis of various 2,5-disubstituted furans is an important pursuit.

The *in situ* generation of 5-aryl-2-(halomethyl) furan **II** from **I** and an activating agent such as PBr_3 and subsequent heteroatom alkylations have been reported (Scheme 1a).⁶ However, the desired products were obtained in moderate yields because of the severe undesired reactions caused by the highly reactive **II**. Continuous synthesis is a scalable, cost- and energy-efficient approach.⁷ In 1979, Hutton *et al.* reported that the chlorination of furfuryl alcohol derivative **I** ($\text{Ar} = 4\text{-ClC}_6\text{H}_4$) using SOCl_2 , followed by the addition of sodium cyanide to the unstable alkyl chloride **IV** using a continuous stirred-tank reactor (CSTR) consists of two 10 mL flasks (Scheme 1b).⁸ This pioneering work demonstrated the high-yielding synthesis of desired **V** (*ca.* 10 kg scale preparation of **V** per week) by controlling the residence time (*ca.* 1 min) of the unstable **IV**.

Rapid *in situ* generation of 2-(halomethyl)-5-phenylfuran and nucleophilic addition in a microflow reactor†

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2,5-Disubstituted furans are frequently found in pharmaceuticals and bioactive natural products. Nucleophilic substitution reactions on the carbon atom adjacent to the furan ring are useful for producing various furan derivatives. However, the formation of 5-substituted 2-halomethylfuran and the subsequent nucleophilic substitution reactions are often limited by severe undesired reactions caused by the highly reactive halomethylfurans. This paper reports the successful rapid synthesis of various 2,5-disubstituted furans using microflow technology, which suppresses undesired reactions including dimerization and ring opening of the furans. We observed that Brønsted acids had a significant effect on the nucleophilic substitution reaction and the use of HBr and HI gave the best results. A plausible mechanism of the Brønsted acid-mediated nucleophilic substitutions in the developed approach was proposed.



Scheme 1 Previously reported and our developed nucleophilic substitution reactions *via* highly reactive and unstable electrophiles. (a) Most conventional approach. (b) SOCl_2 -mediated approach using a continuous stirred-tank reactor. (c) PBr_3 -mediated approach using a microflow reactor. (d) TfOH -mediated approach using a microflow reactor. (e) HBr -mediated approach using a microflow reactor *via* 5-aryl-2-(bromomethyl)furan.

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Microflow syntheses have attracted considerable attention owing to their superiority in controlling short reaction times (<1 s) and temperatures compared to those under batch conditions.⁹ Earlier, we had developed efficient microflow syntheses for generating valuable organic compounds.¹⁰ We recently reported the rapid generation of highly active indolylmethyl electrophile **VII** from alcohol **VI** and PBr_3 , its nucleophilic substitution in a microflow reactor (Scheme 1c).¹¹ We also demonstrated the rapid formation of highly electrophilic carbocation **X** from diarylmethanol derivatives **IX** and TfOH , and the subsequent addition of nucleophiles (Scheme 1d).¹²

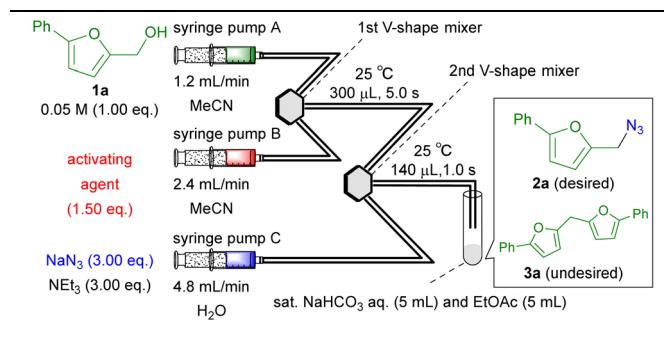
In this study, we synthesized various furan derivatives **III** from alcohols **I** and HBr using microflow to prevent undesired reactions by the highly reactive **XII** (Scheme 1e). The generated **XII** was rapidly used in subsequent nucleophilic substitution reactions. The undesired reactions caused by the coexistence of **I** and **XII** were avoided in the developed process.

The synthesis of azide **2a** from 5-phenyl-2-furanmethanol (**1a**) was investigated (Table 1). Two V-shape mixers with better mixing ability than that of the T-shaped mixer,^{10c} were connected by a Teflon® tube, and the reactor was immersed in a water bath (25 °C). A solution of alcohol **1a** was introduced into the first mixer using syringe pump A, followed by the introduction of a solution containing the activating agent using syringe pump B and alcohol **1a** was rapidly converted into an electrophile. In the second mixer, an aqueous solution of NaN_3 was introduced to initiate nucleophilic substitution. The resulting mixture containing azide **2a** was poured into a

mixture of aqueous solution of sodium bicarbonate and ethyl acetate at 25 °C. The effectiveness of halogenating agents PBr_3 and SOCl_2 used in our previous study¹¹ (Scheme 1c) and Hutton's study⁸ (Scheme 1b) were examined (entries 1 and 2). PBr_3 produced desired product **2a** in high yield (entry 1), whereas SOCl_2 did not (entry 2). Subsequently, we examined the effectiveness of Brønsted acids (entries 3–8) including TfOH , which had afforded the best results (entry 8) for activating diarylmethanols in our previous study (Scheme 1d).¹² When hydrogen halides were used, the yield of the desired **2a** increased as the acidity increased (entries 4, 6, and 7). However, neither H_2SO_4 ($\text{pK}_a = 8.7$) nor TfOH ($\text{pK}_a = 0.7$) gave satisfactory results, irrespective of the acidity (entries 5 and 8). Although the highest yield was obtained with HI aq. (entry 7), HBr aq. was used for subsequent experiments, because it also gave a high yield, and HBr aq. is less expensive and more stable than HI aq.

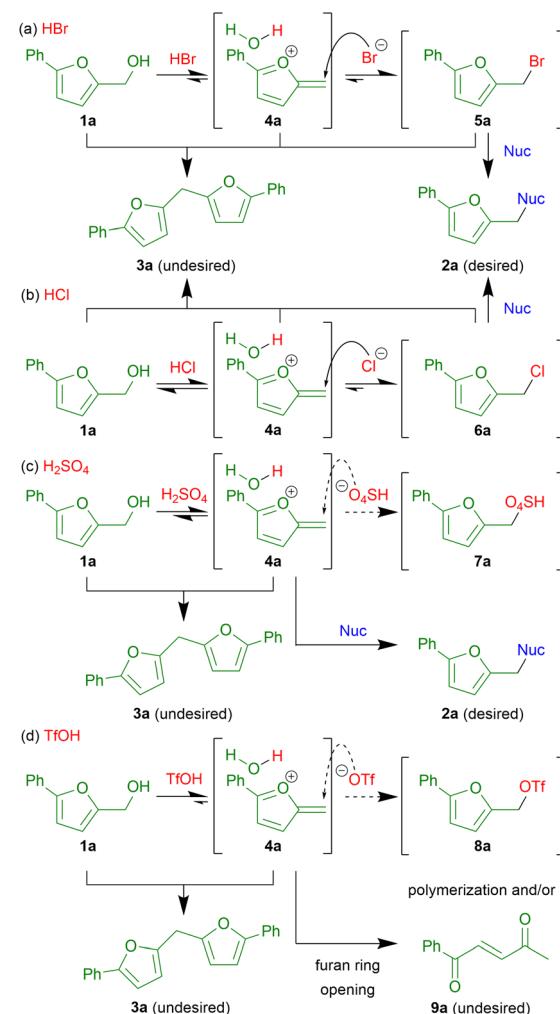
The significant influence of the Brønsted acids on the reaction was observed. The plausible mechanism of Brønsted acid-mediated nucleophilic substitutions is shown in Scheme 2. We

Table 1 Examination of Brønsted acids and bases



Entry	Activating agent (pK_a^a)	Yield ^f [%]		
		2a (desired)	1a (sub)	3a (undesired)
1	PBr_3^b	87	<1	9
2	SOCl_2	2	97	<1
3	AcOH (23.5)13	<1	97	<1
4	HCl^c (10.3)13	8	66	26
5	H_2SO_4 (8.7)14	<1	5	72
6	HBr^d (5.5)13	92	5	3
7	HI^e (2.8)13	95	1	1
8	TfOH (0.7)13	<1	<1	<10

^a pK_a in MeCN. ^b 0.500 eq. of PBr_3 were used. ^c Using HCl aqueous solution (36 w/w%). ^d Using aqueous solution of HBr (47 w/w%). ^e Using aqueous solution of HI (57 w/w%). ^f Yields were determined by ^1H NMR using 1,1,2-trichloroethane. TfOH = trifluoromethanesulfonic acid.

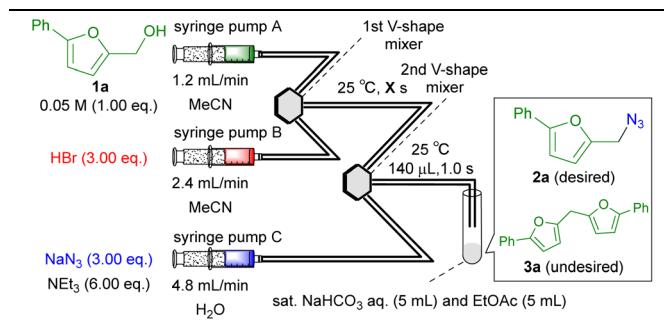


Scheme 2 Plausible mechanisms of (a) HCl -mediated, (b) HBr -mediated, (c) H_2SO_4 -mediated, and (d) TfOH -mediated nucleophilic substitutions.

speculated that the use of highly acidic HBr (and HI) rapidly converts **1a** to the corresponding oxonium ion **4a** (Scheme 2a). Nucleophilic Br^- smoothly attacked highly electrophilic and unstable **4a** to generate metastable alkyl bromide **5a**.¹⁵ This avoided the undesired coexistence of **1a** and **4a** generating undesired dimer **3a**; the nucleophilic substitution of **5a** afforded the desired **2a** in high yield. In contrast, less acidic HCl ($\text{p}K_a = 10.3$) could not rapidly convert **1a** to **4a** (Scheme 2b). In addition, the generation of alkyl chloride **5a** was slow due to the lower nucleophilicity of Cl^- compared to that of Br^- .¹⁶ Thus, the undesired coexistence of **1a** and **4a** caused the generation of **3a**. The low yield obtained using H_2SO_4 , despite its higher acidity than that of HCl, is attributable to the poor nucleophilicity of HSO_4^- (Scheme 2c).¹⁷ This caused the undesired coexistence of **1a** and **4a**. The poor yield obtained using TfOH, which gave the best results in our previously reported activation of diarylmethanols¹² is attributable to the polymerization of **4a** and undesired reactions involving the opening of the furan ring caused by the high acidity of TfOH (Scheme 2d). Murkovic *et al.* and Dumesic *et al.* reported that furfuryl alcohol derivatives undergo polymerization and furan ring-opening reactions in the presence of strong acid.¹⁸

The reaction time for the HBr-mediated activation of **1a** was then investigated (Table 2); the results indicated that decreasing the reaction time to 1.0 s decreased the yield of **2a** (entries 1 vs. 2), whereas increasing the reaction time to 10 s slightly improved the yield (entries 2 vs. 3). Further extension of the reaction time to 60 s did not improve the yield of **2a** (entries 3 vs. 5). Additional examination (for details, see the ESI†)

Table 2 Reaction time for the HBr-mediated activation of **1a**



Entry	X s ^c	Yield ^e [%]		
		2a (desired)	1a (sub)	3a (undesired)
1	1.0	64	34	2
2	5.0	96	2	2
3	10	97	<1	2
4 ^a	10	97 ± 1 (95) ^d	<1	<1
5	60	97	<1	2
6 ^{a,b}	10	51 ± 5	<1	43 ± 1

^a Three independent experiments were performed. ^b Reaction mixture was magnetically stirred (1000 rpm) under batch conditions. ^c The volume of the tubes for the reaction of **1a** with HBr was 60 μL ($X = 1.0$ s), 300 μL ($X = 5.0$ s), 600 μL ($X = 10$ s), and 3600 μL ($X = 60$ s). ^d Isolated yield. ^e Yields were determined by ^1H NMR using 1,1,2-trichloroethane.

enabled the determination of the optimal conditions of the reaction (entry 4). The desired product **2a** was obtained in 97% NMR yield (95% isolated yield) under the optimal conditions. To verify the importance of the microflow conditions, we examined comparative batch conditions, except for the reaction time for the nucleophilic attack of N_3^- (10 s), because performing the batch reaction in 1.0 s (entry 4) was impossible. (Caution: As the reaction is accompanied by the highly exothermic neutralization and potential generation of toxic and explosive HN_3 , batch reaction should be performed with extreme caution. Particularly in scale-up synthesis, the use of batch synthesis should be avoided). Both the yield and reproducibility under batch conditions were lower than those under flow conditions (entries 4 vs. 6). These results clearly indicate the importance of the microflow technology in the developed approach.

Subsequently, the scope of the nucleophiles in the developed approach was examined (Fig. 1). The use of pyrrolidine as a nucleophile produced the desired **2b** in good yield (71%), whereas the use of 2-bromoaniline with weak nucleophilicity produced the desired **2c** in low yield (33%). The use of sulfur nucleophiles afforded the desired **2d**–**2f** in good to high yields (64–90%). The synthesis of **2f** was scaled-up by extending the pumping time (960 s) under higher concentration conditions (0.200 M) to increase productivity. The desired **2f** (0.72 g) was obtained in 63% yield. Although the use of phenol as an oxygen nucleophile afforded a complex mixture, the use of KCN and Meldrum's acid as carbon nucleophiles afforded the desired **2h**¹⁹ and **2i** in acceptable yields (59 and 55%).

The scope of electrophiles was examined (Fig. 2). Compounds **2j** and **2k** containing electron-donating OMe or electron-withdrawing Cl groups on the benzene ring, were obtained in high to excellent yields (86–94%), whereas **2l** con-

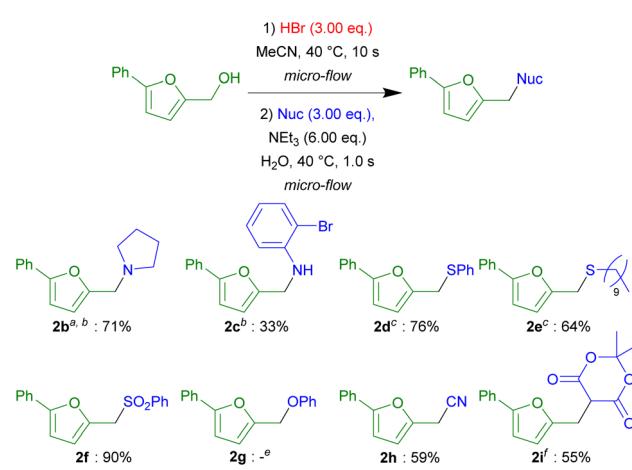


Fig. 1 Scope of nucleophiles ^a 6.0 eq. pyrrolidine was used instead of 6.0 eq. NEt_3 . ^b Nucleophile was dissolved in MeCN instead of H_2O and reaction time of **5a** with the nucleophile was extended to 10 s. ^c Nucleophile was dissolved in MeCN instead of H_2O in the synthesis of **2d** and **2e**. 6.0 eq. of 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) was used instead of 6.0 eq. of NEt_3 in the synthesis of **2e**. ^d 0.200 M of substrate solution was used. ^e Complex mixture was obtained. ^f 3.0 eq. of *t*-BuOK was used for deprotonating Meldrum's acid. 3.0 eq. of NEt_3 was used.



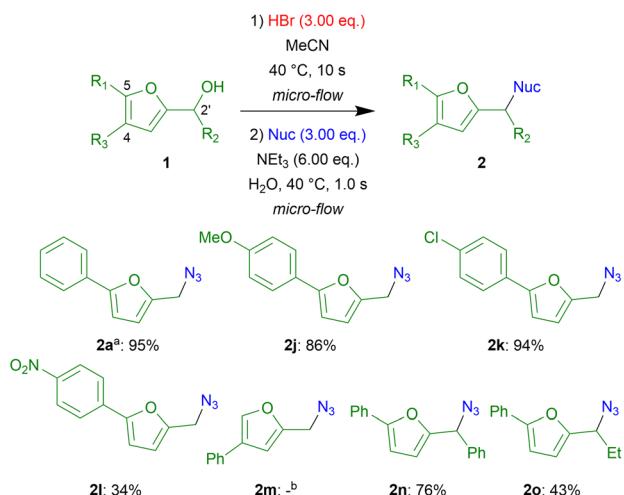


Fig. 2 Examination of the scope of electrophiles. ^aThe yield of **2a** was re-shown to clarify the scope and limitation of electrophiles. ^bComplex mixture was obtained.

taining a strong electron-withdrawing NO_2 group, was obtained in a low yield (34%), presumably due to the slow generation of the electrophilic intermediate. The synthesis of **2m** containing a benzene ring at the 4-position of the furan ring was examined. However, the desired product was not obtained; conversely, a complex mixture was generated. We speculated that an undesired reaction occurred at the 5-position of the furan ring.²⁰ The **2n** and **2o** containing phenyl and ethyl groups at the 2'-position, respectively were obtained in moderate to good yields (76% and 43%). The moderate yield of **2o** was presumably due to competitive dehydrative alkene formation. Although the compounds **2d–2f**, **2h**, and **2i** derived from *S*- and *C*-nucleophiles are stable, the compounds **2a–2c** and **2j–2o** containing amino and N_3 groups, respectively are relatively unstable. In particular, the compound **2o** containing the secondary N_3 group is unstable.

In general, highly basic nucleophiles cannot be used in the acid-mediated activation of alcohols and subsequent nucleophilic substitution reactions because the acid deactivates the nucleophiles. Therefore, low-basicity nucleophiles, such as amides, imines, and anilines, have often been employed. However, the developed approach can introduce basic amines, rendering it a complementary approach to conventional methods. In addition, although preparations²¹ and uses²² of 5-nonsubstituted furfuryl bromides have been reported, the preparation and use of 5-aryl-substituted furfuryl bromides have been challenging, as previously described. From this perspective too, the developed approach complements conventional approaches.

Conclusions

We developed a method for the rapid (11 or 20 s) nucleophilic substitution reaction at the adjacent carbon of the furan ring. Brønsted acids significantly influence the nucleophilic substi-

tution and the use of HI and HBr afforded the best results. We speculate that the strong acid-induced rapid generation of highly electrophilic and unstable intermediates and the nucleophilic Br^- and I^- smoothly attacked the intermediate to generate a metastable alkyl halide intermediate. This avoids the undesired coexistence of the alcohol and electrophilic intermediate, thus preventing the generation of undesired dimers. Interestingly, TfOH, which afforded the best results in our previously reported activation of diarylmethanols, did not yield the desired product. This is probably because the strongly acidic TfOH induces the decomposition of the furan ring. We demonstrate the importance of microflow technology in the developed approach. In addition, the developed approach complements existing conventional approaches. The developed approach could be utilized for producing various 2,5-disubstituted furans, which could lead to the potential development of furan-based drug candidates and functional materials.

Conflicts of interest

There are no conflicts to declare.

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