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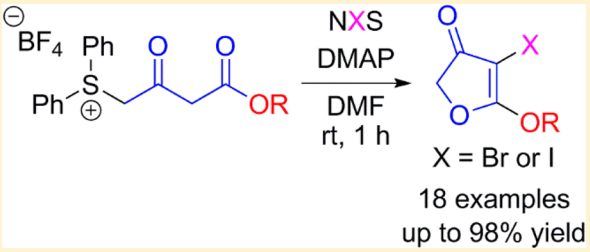
# Synthesis of 4-Halo-3(2*H*)-furanones Using Intramolecular Cyclization of Sulfonium Salts

Sho Inagaki, Maiko Nakazato, Nozomi Fukuda, Satoru Tamura, and Tomikazu Kawano*

Department of Medicinal and Organic Chemistry, School of Pharmacy, Iwate Medical University, Yahaba, Iwate 028-3694, Japan

Supporting Information

**ABSTRACT:** A simple and efficient synthesis of 4-halo-3(2*H*)-furanones by halogenative intramolecular cyclization of sulfonium salts is described, which can expedite the production of a variety of 4-bromo- or 4-iodo-3(2*H*)-furanones, useful synthetic building blocks, in good to high yield under mild conditions.

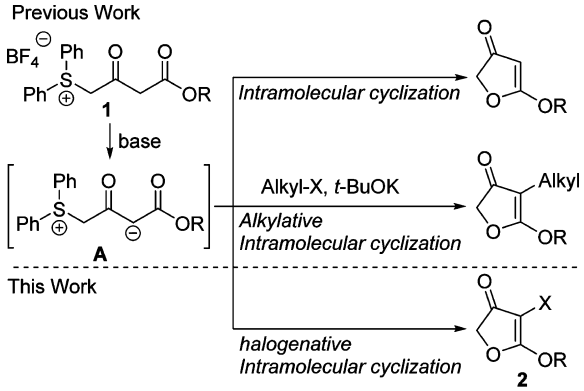



## INTRODUCTION

The polysubstituted 3(2*H*)-furanone structure is a significant moiety present in biologically active substances and natural products.[1] These structures have been reported to exhibit a range of bioactivities such as antitumor,[2] antiallergy,[3] antiulcer,[4] antiproliferation,[5] selective COX-2 inhibiton,[6] and selective MAO-B inhibition activities.[7] A number of synthetic methodologies have been developed for the construction of functionalized 3(2*H*)-furanones.[8,9] Among functionalized 3(2*H*)-furanones, those possessing a halogen group at the 4-position serve as the useful substances. For example, 4-[3-(3-fluorophenyl)-4,5-dihydro-5,5-dimethyl-4-oxo-2-furanyl]benzenesulfonamide (Polmacoxib), known as a cyclooxygenase-2 inhibitor, has been synthesized using 5-aryl-4-bromo-3(2*H*)-furanone as a key synthetic intermediate.[10] However, few synthetic methods have been reported, except for the bromination of the carbon−carbon double bond in 3(2*H*)-furanone[10] or the cyclization/1,2-migration of 2-alkynyl-2-silyloxycarbonyl compounds.[11] Therefore, the development of new approaches for the construction of 4-halo-3(2*H*)-furanones is desired.

We previously reported a synthetic methodology for the construction of a 3(2*H*)-furanone ring via intramolecular cyclization of 3-alkoxycarbonyl-2-oxopropyldiphenylsulfonium tetrafluoroborate (**1**) (Scheme 1).[12] The reaction involves an enolate intermediate (**A**), generated by the treatment of the sulfonium salt (**1**) with a base, which is trapped by electrophiles like alkyl halides (Alkyl-X). While considering the mechanism of our reaction, we believed that the use of an electrophilic halogenating reagent instead of an alkylating reagent would produce the 4-halo-3(2*H*)-furanones (**2**). In this paper, we report an efficient synthesis of 4-halo-3(2*H*)-furanones via halogenative intramolecular cyclization of sulfonium salts. This procedure is simple in handling, and can be expedited using commercially available reagents to give 4-halogenated-3(2*H*)-furanones as synthetic intermediates under mild conditions.

**Scheme 1. Intramolecular Cyclization of Sulfonium Salt 1**




## RESULTS AND DISCUSSION

We began the investigation of halogenative intramolecular cyclization with 3-ethoxycarbonyl-2-oxopropyldiphenylsulfonium tetrafluoroborate (**1A**) as the substrate, and *N*-bromophthalimide (NBP) as the halogenating reagent in THF. Although the reaction was carried out with 2.0 equiv of *t*-BuOK according to our previously reported reaction conditions,[12] the desired product, 4-bromo-5-ethoxy-3(2*H*)-furanone **2aA**, was not obtained. Fortunately, decreasing the amount of *t*-BuOK to 1.0 equiv afforded **2aA** in 26% yield (Table 1, entry 1). Encouraged by this result, we examined several other base reagents. The use of inorganic bases such as $K_2CO_3$, or the absence of a base, produced **2aA** in still lower yields (entries 2 and 3). Experimental evidence indicated that the presence of an appropriately selected nucleophilic amine furthered the progress of the reaction, because the reaction gave a better yield in the presence of triethylamine ($Et_3N$) than a bulkier

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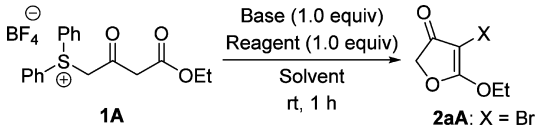
**Table 1. Optimized Reaction Conditions**[a]

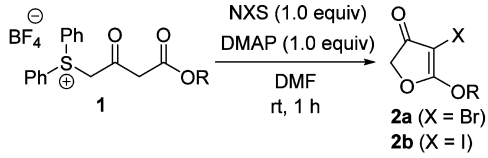



| entry | base | solvent | reagent | 2 | yield (%)[b] |
|---|---|---|---|---|---|
| 1 | *t*-BuOK | THF | NBP | **2aA** | 26 |
| 2 | $K_2CO_3$ | THF | NBP | **2aA** | 19 |
| 3 | none | THF | NBP | **2aA** | 15 |
| 4 | DIPEA | THF | NBP | **2aA** | 47 |
| 5 | $Et_3N$ | THF | NBP | **2aA** | 63 |
| 6 | pyridine | THF | NBP | **2aA** | 33 |
| 7 | imidazole | THF | NBP | **2aA** | 57 |
| 8 | DMAP | THF | NBP | **2aA** | 68 |
| 9 | DMAP | toluene | NBP | **2aA** | 26 |
| 10 | DMAP | $CH_2Cl_2$ | NBP | **2aA** | 60 |
| 11 | DMAP | MeCN | NBP | **2aA** | 62 |
| 12 | DMAP | acetone | NBP | **2aA** | 73 |
| 13 | DMAP | DMF | NBP | **2aA** | 76 |
| 14 | DMAP | DMF | NBSac | **2aA** | 60 |
| 15 | DMAP | DMF | NBA | **2aA** | 67 |
| 16 | DMAP | DMF | NBS | **2aA** | 82 |
| 17 | DMAP | DMF | $Br_2$ | **2aA** | 0 |
| 18 | DMAP | DMF | BDMS | **2aA** | 0 |
| 19 | DMAP | DMF | NIS | **2bA** | 83 |
| 20 | DMAP | DMF | NCS | **2cA** | 0 |
| 21 | DMAP | DMF | Selectfluor | **2dA** | 0 |

[a]Reaction conditions: sulfonium salt **1A** (0.2 mmol), reagent (1.0 equiv), and base (1.0 equiv) in solvent (1.0 mL). DIPEA = *N*,*N*-diisopropylethylamine, DMAP = 4-dimethylaminopyridine, NBP = *N*-bromophthalimide, NBSac = *N*-bromosaccharin, NBA = *N*-bromoacetamide, NBS = *N*-bromosuccinimide, BDMS = bromodimethylsulfonium bromide, NIS = *N*-iodosuccinimide, NCS = *N*-chlorosuccinimide. [b]The product was purified by silica-gel column chromatography and the isolated yield based on **1A**.

With optimized reaction conditions in hand, we set out to investigate the substrate scope and limitations of the halogenative intramolecular cyclization (Table 2). Initially, the

**Table 2. Substrate Scope and Limitations**[a]




**1A**: R = Et **1D**: R = Cyclohexyl **1G**: R = Ph
**1B**: R = *i*Pr **1E**: R = Allyl **1H**: R = Bn
**1C**: R = Cyclopentyl **1F**: R = Propargyl **1I**: R = 4-$BrC_6H_4CH_2$

| entry | 1 | NXS | 2 | yield (%)[b] |
|---|---|---|---|---|
| 1 | **1A** | NBS | **2aA** | 82 |
| 2 | **1B** | NBS | **2aB** | 86 |
| 3 | **1C** | NBS | **2aC** | 72 |
| 4 | **1D** | NBS | **2aD** | 83 |
| 5 | **1E** | NBS | **2aE** | 60 |
| 6 | **1F** | NBS | **2aF** | 73 |
| 7 | **1G** | NBS | **2aG** | 75 |
| 8 | **1H** | NBS | **2aH** | 71 |
| 9 | **1I** | NBS | **2aI** | 76 |
| 10 | **1A** | NIS | **2bA** | 83 |
| 11 | **1B** | NIS | **2bB** | 98 |
| 12 | **1C** | NIS | **2bC** | 97 |
| 13 | **1D** | NIS | **2bD** | 91 |
| 14 | **1E** | NIS | **2bE** | 80 |
| 15 | **1F** | NIS | **2bF** | 96 |
| 16 | **1G** | NIS | **2bG** | 87 |
| 17 | **1H** | NIS | **2bH** | 84 |
| 18 | **1I** | NIS | **2bI** | 90 |

[a]Reaction conditions: sulfonium salt **1** (0.2 mmol), NXS (1.0 equiv), and DMAP (1.0 equiv) in DMF (1.0 mL). NBS = *N*-bromosuccinimide, NIS = *N*-iodosuccinimide. [b]The residue was purified by silica-gel column chromatography and the isolated yield based on **1**.

base, *N*,*N*-diisopropylethylamine (DIPEA) (entries 4 and 5). Among the examined nucleophilic amines, 4-dimethylaminopyridine (DMAP) was the most productive, resulting in a 68% yield of **2aA** (entry 8).

Next, we investigated the solvent effect on this reaction (entries 9−13). The results revealed that polar aprotic solvents were crucial for the reaction: *N*,*N*-dimethylformamide (DMF) produced **2aA** in 76% yield. These results of the solvent studies probably depended on the solubility of sulfonium salt **1A**. Other brominating reagents were also examined (entries 14−18). Among the examined reagents, i.e., *N*-bromosaccharin (NBSac), *N*-bromosuccinimide (NBS), and *N*-bromoacetamide (NBA), NBS produced **2aA** in the highest yield (entry 16), whereas bromine[13] and bromodimethylsulfonium bromide (BDMS),[14] employed in the bromination reaction of the active methylene moiety in 1,3-dicarbonyl compounds, failed to produce **2aA** (entries 17 and 18). The iodination reaction by *N*-iodosuccinimide (NIS) as another halogen source proceeded successfully to afford 4-iodo-5-ethoxy-3(2*H*)-furanone **2bA** in 83% yield (entry 19). However, *N*-chlorosuccinimide (NCS) and chloromethyl-4-fluoro-1,4-diazoniabicyclo[2.2.2]octane bis(tetrafluoroborate) (Selectfluor) could not be applied to the reaction (entries 20 and 21).

reactions of the sulfonium salts **1** were carried out with NBS and DMAP in DMF. The sufonium salts **1** bearing ethyl, isopropyl, cyclopentyl, or cyclohexyl esters underwent brominative intramolecular cyclization to give the corresponding 4-bromo-5-alkoxy-3(2*H*)-furanones **2aA**−**2aD** in good to high yields (entries 1−4). Interestingly, sulfonium salts **1** bearing allyl and propargyl moieties produced 4-bromo-3(2*H*)-furanones bearing allyloxy (**2aE**) and propargyloxy (**2aF**) groups at the 5-position in 60% and 73% yields, respectively (entries 5 and 6). Although carbon−carbon double or triple bonds are generally reactive for NBS, brominative intramolecular cyclization of **1E** and **1F** proceeded successfully under the reaction conditions. Moreover, the reactions using phenyl, benzyl, and 4-bromobenzyl groups also worked well (entries 7−9). We also examined the reaction using NIS; the desired 4-iodo-3(2*H*)-furanones were obtained in higher yields in all of the cases (entries 10−18), compared to the corresponding 4-bromo products. It is noteworthy that all the reactions were complete within 1 h at room temperature and were achieved using common and inexpensive reagents: NBS, NIS, and DMAP.

To determine the detailed reaction mechanism, a $^1$H NMR study was initiated. It had been previously reported that NIS



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formed a coordination complex with DMAP, and the resulting $^1$H NMR signal at 3.04 ppm (in $CDCl_3$) was shifted upfield,[15] whereas NBS was reported to be inactivated by DMAP to form a coordination complex.[16] However, from the results shown in Table 2, we hypothesized that NBS might also form a complex with DMAP. In $CDCl_3$, the chemical shift of the methylene protons of NBS was 2.97 ppm, while the signal was shifted upfield to 2.81 ppm in the equimolar mixture of NBS and DMAP after 10 min of mixing (Figure 1a,b). This upfield shift of methylene protons in NBS closely resembled that in NIS. The signal at 3.03 ppm from NIS was shifted to 2.74 ppm as the signal in the 1:1 mixture of NIS and DMAP (Figure S1), which was consistent with reported data.[15] Thus, the observation of signal shift suggests that NBS is activated by DMAP as well as NIS. In contrast, NCS did not seem to form a complex with DMAP, because no change in chemical shift was observed upon mixing with DMAP (Figure 1c,d). Additionally, in the mixture of NIS or NBS with various amounts of DMAP (0.2−1.0 equiv), we observed an ambiguous broad signal, and sequential upfield shifts of signal corresponding to the amount of DMAP; however, no such observation was made in the mixture of NCS with DMAP (Figures S2−S4). These results of the $^1$H NMR study agreed well with the reactivity of **1A** with *N*-halosuccinimide (NXS) and DMAP in $CDCl_3$; NBS and NIS provided the corresponding 4-halogenated products **2aA** and **2bA**, respectively, but NCS did not give any 4-chlorinated product **2cA** under the same conditions (Scheme 2). The treatment of **1A** with DMAP in the absence of NXS afforded the only not halogenated cyclization product, 5-ethoxy-3(2*H*)-furanone.[12] All of the results mentioned above revealed that an equimolar complex of NIS or NBS with DMAP is essential for the reaction.

On the basis of all the results described above, a plausible mechanism for the halogenative intramolecular cyclization of sulfonium salt **1** is postulated in Scheme 3. Initially, NXS was activated by an equimolar amount of DMAP to form a coordination complex **B**. The deprotonation of **1** generated enolate **A** and succinimide. The nucleophilic attack of the resultant enolate **A** on the electron-deficient halogen atom generated a 3-halogenated sulfonium salt **C** and DMAP. Subsequently, enolate **D** produced by deprotonation of **C** with the regenerated DMAP underwent a cyclization to give 5-alkoxy-4-halo-3(2*H*)-furanone **2**.

We executed the scale-up of the halogenative intermolecular cyclization to demonstrate the potential benefit of this synthetic method. The reaction of the sulfonium salts **1A** and **1F** (5.0 mmol) with equimolar amounts of NXS and DMAP in DMF (10 mL) at room temperature was completed within 1 h to give the corresponding 4-halo-3(2*H*)-furanones **2aA**, **2aF**, **2bA**, and **2bF** with good to high yields (Scheme 4).

For further evaluation of the synthetic utility of this protocol, we undertook Pd-catalyzed coupling reactions using 4-iodo-3(2*H*)-furanone **2bA** as the substrate (Scheme 5). The Suzuki−Miyaura coupling reactions of **2bA** with 1.5 equiv of arylboronic acids in the presence of 5 mol % of $Pd(OAc)_2$ and 3.0 equiv of CsF, at 40 °C for 21 h, afforded 4-aryl-5-ethoxy-3(2*H*)-furanones (**3**) in high yields (eq 1). The Sonogashira−Hagiwara coupling reactions of **2bA** with 2.0 equiv of terminal alkynes in the presence of 3 mol % of $Pd(PPh_3)_2Cl_2$ and 10 mol % of CuI gave 4-alkynyl-5-ethoxy-3(2*H*)-furanones (**4**) with good to high yields (eq 2). Furthermore, 5 mol % of $Pd(PPh_3)_4$ was used to catalyze the Migita−Kosugi−Stille coupling reaction of **2bA** with 1.0 equiv of tri(*n*-butyl)vinyltin, which afforded 5-ethoxy-4-vinyl-3(2*H*)-furanone (**5**) in 61% yield. Thus, the transformations of **2bA** furnished 3(2*H*)-furanone derivatives bearing alkynyl, alkenyl, and aryl groups at the 4-position, indicating that 4-halo-3(2*H*)-furanones play a vital role in the reactions.

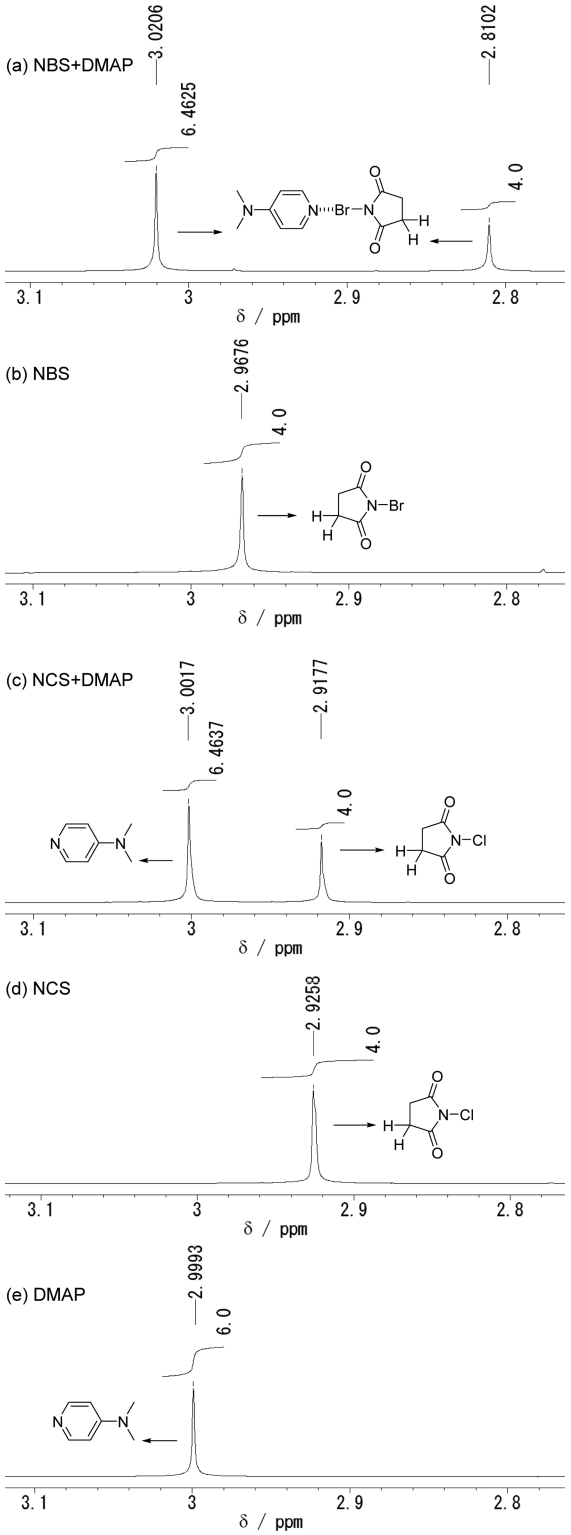


**Figure 1.** $^1$H NMR spectra of (a) an equimolar mixture of NBS and DMAP after 10 min of mixing, (b) NBS only, (c) an equimolar mixture of NCS and DMAP after 10 min of mixing, (d) NCS only, and (e) DMAP only.



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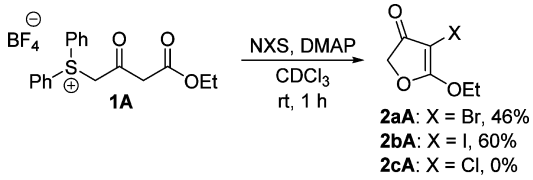
**Scheme 2. Halogenative Intramolecular Cyclization of 1A with Equimolar Amounts of NXS and DMAP in $CDCl_3$**




## CONCLUSION

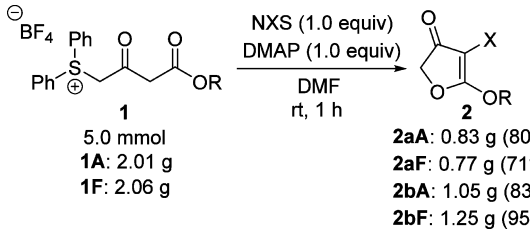
In summary, we have developed the synthesis of 4-bromo- or 4-iodo-3(2*H*)-furanones from sulfonium salts via halogenation, followed by intramolecular cyclization under mild conditions. We clarified some substrate scopes and the functional group tolerances of the reaction. A coordination complex was prepared from an equimolar mixture of DMAP and *N*-halosuccinimides when NBS or NIS was involved in this reaction. Furthermore, 4-iodo-3(2*H*)-furanones could be subjected to Pd-catalyzed coupling reactions and converted into 3(2*H*)-furanone derivatives possessing alkynyl, alkenyl, and aryl groups at the 4-position. This methodology could supply novel synthetic intermediates for the preparation of compounds with relevant molecular frameworks.

## EXPERIMENTAL SECTION

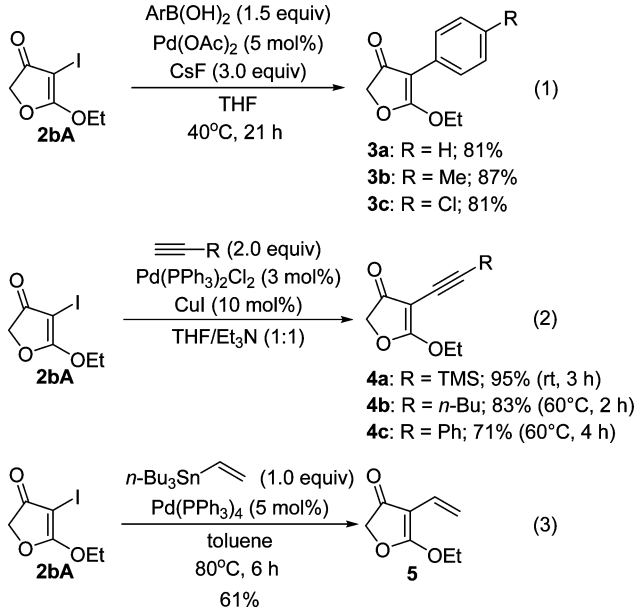
All reactions were performed under an argon atmosphere. The reagents and solvents were used as received from commercial suppliers without any further purification, unless otherwise indicated. Sulfonium salt **1** was prepared according to our reported method.[12] NBS was recrystallized from hot water. $Et_3N$ was distilled over calcium hydride. Silica gel (40−50 mesh) was used for flash column chromatography. Components separated by thin-layer chromatography (TLC) were detected under UV light at 254 nm or by staining with ethanoic *p*-anisaldehyde. IR spectra were recorded on an FT-IR spectrometer. $^1H$ and $^{13}C$ NMR spectra recorded in $CDCl_3$ were referenced to TMS (0.00 ppm) and the solvent peak (77.0 ppm). High-resolution mass spectra (HRMS) were obtained using an electrospray ionization time-of-flight (ESI-TOF) mass spectrometer.

**General Procedure for Synthesis of 5-Alkoxy-4-halo-3(2*H*)-furanones (2).** 4-Dimethylaminopyridine (DMAP) (24.5 mg, 0.20 mmol) and *N*-halosuccinimide (1.0 equiv) were added to a solution of sulfonium salt **1** (0.20 mmol) in dry DMF (1.0 mL) at room temperature, and the mixture was stirred for 1 h. The mixture was treated with water and extracted with EtOAc. The organic extract was washed with an aqueous solution of 0.5 M $Na_2S_2O_3$, water (three times), and brine. The organic extract was dried over anhydrous $Na_2SO_4$ and concentrated under reduced pressure. Purification by flash column chromatography on silica gel (*n*-hexane/EtOAc = 1:1) gave the desired 5-alkoxy-4-halo-3(2*H*)-furanone **2**.

**Scheme 4. Large-Scale Synthesis**



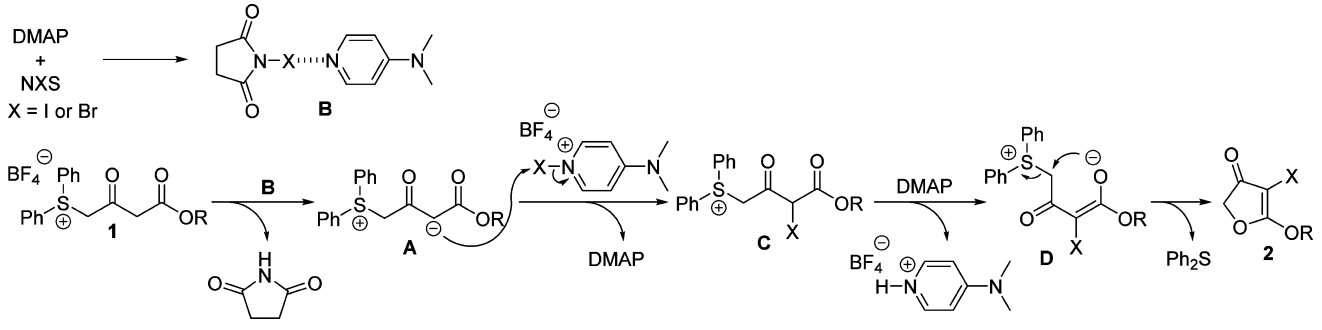

**Scheme 5. Transformation of 4-Iodo-3(2*H*)-furanone 2bA**




*4-Bromo-5-ethoxy-3(2H)-furanone* (***2aA***). 34.1 mg, 82% yield; pale yellow solid; mp 76.8−77.5 °C; $R_f$ = 0.38 (*n*-hexane/EtOAc = 1:2); IR (KBr): 1700, 1599 $cm^{-1}$; $^1H$ NMR (500 MHz, $CDCl_3$): $\delta$ 4.74 (s, 2 H), 4.56 (q, $J$ = 7.1 Hz, 2 H), 1.50 (t, $J$ = 7.1 Hz, 3 H); $^{13}C$ NMR (126 MHz, $CDCl_3$): $\delta$ 189.8, 179.8, 75.4, 72.2, 67.5, 14.7; HRMS (ESI-TOF): $m/z$ [M + Na]$^+$ calcd for $C_6H_7Br^{81}NaO_3$, 230.9451; found, 230.9446; calcd for $C_6H_7Br^{79}NaO_3$, 228.9471; found, 228.9472.

*4-Bromo-5-isopropyloxy-3(2H)-furanone* (***2aB***). 38.2 mg, 86% yield; pale yellow solid; mp 90.4−90.5 °C; $R_f$ = 0.44 (*n*-hexane/EtOAc = 1:2); IR (KBr): 1690, 1584 $cm^{-1}$; $^1H$ NMR (500 MHz, $CDCl_3$): $\delta$ 5.23 (sept, $J$ = 6.2 Hz, 1 H), 4.73 (s, 2 H), 1.47 (d, $J$ = 6.2 Hz, 6 H); $^{13}C$ NMR (126 MHz, $CDCl_3$): $\delta$ 189.9, 179.5, 76.9, 75.2, 72.4, 22.3; HRMS (ESI-TOF): $m/z$ [M + Na]$^+$ calcd for $C_7H_9Br^{81}NaO_3$, 244.9607; found, 244.9607; calcd for $C_7H_9Br^{79}NaO_3$, 242.9627; found, 242.9623.

**Scheme 3. A Plausible Mechanism**



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*4-Bromo-5-cyclopentyloxy-3(2H)-furanone* (**2aC**). 35.6 mg, 72% yield; pale yellow solid; mp 89.9−90.3 °C; $R_f$ = 0.50 (*n*-hexane/EtOAc = 1:2); IR (KBr): 2955, 1696, 1596 $cm^{-1}$; $^1H$ NMR (500 MHz, $CDCl_3$): $\delta$ 5.42−5.39 (m, 1 H), 4.72 (s, 2 H), 1.99−1.95 (m, 4 H), 1.90−1.82 (m, 2 H), 1.72−1.64 (m, 2 H); $^{13}C$ NMR (126 MHz, $CDCl_3$): $\delta$ 189.9, 179.6, 85.6, 75.3, 72.6, 33.2, 23.5; HRMS (ESI-TOF): *m*/*z* $[M + Na]^+$ calcd for $C_9H_{11}Br^{81}NaO_3$, 270.9764; found, 270.9766; calcd for $C_9H_{11}Br^{79}NaO_3$, 268.9784; found, 268.9783.

*4-Bromo-5-cyclohexyloxy-3(2H)-furanone* (**2aD**). 43.3 mg, 83% yield; pale yellow solid; mp 59.9−60.6 °C; $R_f$ = 0.56 (*n*-hexane/EtOAc = 1:2); IR (KBr): 2941, 1698, 1577 $cm^{-1}$; $^1H$ NMR (500 MHz, $CDCl_3$): $\delta$ 5.00−4.95 (m, 1 H), 4.71 (s, 2 H), 2.01−1.97 (m, 2 H), 1.87−1.82 (m, 2 H), 1.74−1.67 (m, 2 H), 1.60−1.54 (m, 1 H), 1.45−1.32 (m, 3 H); $^{13}C$ NMR (126 MHz, $CDCl_3$): $\delta$ 189.9, 179.5, 81.3, 75.2, 72.4, 31.8, 24.8, 23.2; HRMS (ESI-TOF): *m*/*z* $[M + Na]^+$ calcd for $C_{10}H_{13}Br^{81}NaO_3$, 284.9921; found, 284.9915; calcd for $C_{10}H_{13}Br^{79}NaO_3$, 282.9940; found, 282.9945.

*5-Allyloxy-4-bromo-3(2H)-furanone* (**2aE**). Compound **2aE** was sensitive to moisture and acid. The flask containing **2aE** was immediately filled with an argon and stored at −20 °C. 26.3 mg, 60% yield; yellow oil; $R_f$ = 0.52 (*n*-hexane/EtOAc = 1:2); IR (neat): 1704, 1586 $cm^{-1}$; $^1H$ NMR (500 MHz, $CDCl_3$): $\delta$ 6.02 (ddq, *J* = 17.1, 10.5, 5.9 Hz, 1 H), 5.49 (dq, *J* = 17.1, 1.3 Hz, 1 H), 5.43 (dq, *J* = 10.5, 1.3 Hz, 1 H), 4.96 (dt, *J* = 5.9, 1.3 Hz, 2 H), 4.75 (s, 2 H); $^{13}C$ NMR (126 MHz, $CDCl_3$): $\delta$ 189.9, 179.6, 129.9, 121.1, 75.5, 72.5, 71.3; HRMS (ESI-TOF): *m*/*z* $[M - CH_2CH{=}CH_2]^-$ calcd for $C_4H_2Br^{81}O_3$, 178.9173; found, 178.9179; calcd for $C_4H_2Br^{79}O_3$, 176.9193; found, 176.9199.

*4-Bromo-5-propargyloxy-3(2H)-furanone* (**2aF**). 31.6 mg, 73% yield; pale yellow solid; mp 105.0−105.4 °C; $R_f$ = 0.48 (*n*-hexane/EtOAc = 1:2); IR (KBr): 2122, 1693, 1587 $cm^{-1}$; $^1H$ NMR (500 MHz, $CDCl_3$): $\delta$ 5.06 (d, *J* = 2.4 Hz, 2 H), 4.79 (s, 2 H), 2.71 (t, *J* = 2.4 Hz, 1 H); $^{13}C$ NMR (126 MHz, $CDCl_3$): $\delta$ 190.0, 179.1, 78.1, 75.8, 75.2, 73.3, 57.9; HRMS (ESI-TOF): *m*/*z* $[M + Na]^+$ calcd for $C_7H_5Br^{81}NaO_3$, 240.9294; found, 240.9290; calcd for $C_7H_5Br^{79}NaO_3$, 238.9314; found, 238.9309.

*4-Bromo-5-phenyloxy-3(2H)-furanone* (**2aG**). 38.3 mg, 75% yield; pale yellow solid; mp 173.8−174.3 °C; $R_f$ = 0.58 (*n*-hexane/EtOAc = 1:2); IR (KBr): 1698, 1572 $cm^{-1}$; $^1H$ NMR (500 MHz, $CDCl_3$): $\delta$ 7.47−7.44 (m, 2 H), 7.37−7.34 (m, 1 H), 7.24−7.22 (m, 2 H), 4.75 (s, 2 H); $^{13}C$ NMR (126 MHz, $CDCl_3$): $\delta$ 190.4, 178.7, 150.8, 129.9, 127.2, 120.5, 75.6, 74.2; HRMS (ESI-TOF): *m*/*z* $[M + Na]^+$ calcd for $C_{10}H_7Br^{81}NaO_3$, 278.9451; found, 278.9449; calcd for $C_{10}H_7Br^{79}NaO_3$, 276.9471; found, 276.9467.

*5-Benzyloxy-4-bromo-3(2H)-furanone* (**2aH**). 38.2 mg, 71% yield; pale yellow solid; mp 65.6−66.5 °C; $R_f$ = 0.40 (*n*-hexane/EtOAc = 1:2); IR (KBr): 1699, 1594 $cm^{-1}$; $^1H$ NMR (500 MHz, $CDCl_3$): $\delta$ 7.44−7.41 (m, 5 H), 5.48 (s, 2 H), 4.75 (s, 2 H); $^{13}C$ NMR (126 MHz, $CDCl_3$): $\delta$ 189.9, 179.7, 133.3, 129.4, 129.0, 128.4, 75.6, 72.7, 72.4; HRMS (ESI-TOF): *m*/*z* $[M + Na]^+$ calcd for $C_{11}H_9Br^{81}NaO_3$, 292.9608; found, 292.9616; calcd for $C_{10}H_7Br^{79}NaO_3$, 290.9627; found, 290.9621.

*4-Bromo-5-(4-bromobenzyl)oxy-3(2H)-furanone* (**2aI**). 52.9 mg, 76% yield; pale yellow solid; mp 110.0−110.7 °C; $R_f$ = 0.48 (*n*-hexane/EtOAc = 1:2); IR (KBr): 1701, 1590 $cm^{-1}$; $^1H$ NMR (500 MHz, $CDCl_3$): $\delta$ 7.57 (d, *J* = 8.3 Hz, 2 H), 7.30 (d, *J* = 8.3 Hz, 2 H), 5.43 (s, 2 H), 4.75 (s, 2 H); $^{13}C$ NMR (126 MHz, $CDCl_3$): $\delta$ 189.8, 179.5, 132.3, 132.2, 130.0, 123.7, 75.6, 72.9, 71.5; HRMS (ESI-TOF): *m*/*z* $[M + Na]^+$ calcd for $C_{11}H_8Br^{81}Br^{79}NaO_3$, 370.8712; found, 370.8707; calcd for $C_{10}H_7Br^{79}{}_2NaO_3$, 368.8732; found, 368.8739.

*5-Ethoxy-4-iodo-3(2H)-furanone* (**2bA**). 42.2 mg, 83% yield; pale yellow solid; mp 91.2−91.5 °C (dec.); $R_f$ = 0.48 (*n*-hexane/EtOAc = 1:2); IR (KBr): 1698, 1571 $cm^{-1}$; $^1H$ NMR (500 MHz, $CDCl_3$): $\delta$ 4.78 (s, 2 H), 4.55 (q, *J* = 7.1 Hz, 2 H), 1.49 (t, *J* = 7.1 Hz, 3 H); $^{13}C$ NMR (126 MHz, $CDCl_3$): $\delta$ 192.6, 181.8, 75.6, 67.5, 40.0, 14.7; HRMS (ESI-TOF): *m*/*z* $[M + Na]^+$ calcd for $C_6H_7INaO_3$, 276.9332; found, 276.9336.

*5-Isopropyloxy-4-iodo-3(2H)-furanone* (**2bB**). 52.6 mg, 98% yield; pale yellow solid; mp 84.5−84.9 °C; $R_f$ = 0.54 (*n*-hexane/EtOAc = 1:2); IR (KBr): 1680, 1570 $cm^{-1}$; $^1H$ NMR (500 MHz, $CDCl_3$): $\delta$ 5.22 (sept, *J* = 6.2 Hz, 1 H), 4.77 (s, 2 H), 1.47 (d, *J* = 6.2 Hz, 6 H); $^{13}C$ NMR (126 MHz, $CDCl_3$): $\delta$ 192.6, 181.5, 76.8, 75.4, 40.4, 22.3; HRMS (ESI-TOF): *m*/*z* $[M + Na]^+$ calcd for $C_7H_9INaO_3$, 290.9489; found, 290.9490.

*5-Cyclopentyloxy-4-iodo-3(2H)-furanone* (**2bC**). 57.2 mg, 97% yield; pale yellow solid; mp 78.2−79.0 °C; $R_f$ = 0.60 (*n*-hexane/EtOAc = 1:2); IR (KBr): 2951, 1685, 1577 $cm^{-1}$; $^1H$ NMR (500 MHz, $CDCl_3$): $\delta$ 5.41−5.38 (m, 1 H), 4.77 (s, 2 H), 1.98−1.94 (m, 4 H), 1.90−1.82 (m, 2 H), 1.72−1.64 (m, 2 H); $^{13}C$ NMR (126 MHz, $CDCl_3$): $\delta$ 192.6, 181.6, 85.5, 75.5, 40.5, 33.2, 23.5; HRMS (ESI-TOF): *m*/*z* $[M + Na]^+$ calcd for $C_9H_{11}INaO_3$, 316.9645; found, 316.9644.

*5-Cyclohexyloxy-4-iodo-3(2H)-furanone* (**2bD**). 56.3 mg, 91% yield; pale yellow solid; mp 77.5−78.3 °C; $R_f$ = 0.64 (*n*-hexane/EtOAc = 1:2); IR (KBr): 2945, 1686, 1577 $cm^{-1}$; $^1H$ NMR (500 MHz, $CDCl_3$): $\delta$ 5.00−4.95 (m, 1 H), 4.76 (s, 2 H), 2.00−1.95 (m, 2 H), 1.86−1.81 (m, 2 H), 1.74−1.67 (m, 2 H), 1.57−1.54 (m, 1 H), 1.46−1.36 (m, 3 H); $^{13}C$ NMR (126 MHz, $CDCl_3$): $\delta$ 192.6, 181.5, 81.2, 75.4, 40.4, 31.8, 24.9, 23.2; HRMS (ESI-TOF): *m*/*z* $[M + Na]^+$ calcd for $C_{10}H_{13}INaO_3$, 330.9802; found, 330.9802.

*5-Allyloxy-4-iodo-3(2H)-furanone* (**2bE**). Compound **2bE** was sensitive to moisture and acid. The flask containing **2aE** was immediately filled with argon and stored at −20 °C. 42.4 mg, 80% yield; yellow oil; $R_f$ = 0.60 (*n*-hexane/EtOAc = 1:2); IR (neat): 1697, 1574 $cm^{-1}$; $^1H$ NMR (500 MHz, $CDCl_3$): $\delta$ 6.05−5.97 (m, 1 H), 5.50−5.47 (m, 1 H), 5.43−5.41 (m, 1 H), 4.95 (dt, *J* = 5.8, 1.3 Hz, 2 H), 4.79 (s, 2 H); $^{13}C$ NMR (126 MHz, $CDCl_3$): $\delta$ 192.6, 181.6, 130.0, 120.9, 75.7, 71.2, 40.3; HRMS (ESI-TOF): *m*/*z* $[M - CH_2CH{=}CH_2]^-$ calcd for $C_4H_2IO_3$, 224.9054; found, 224.9053.

*4-Iodo-5-propargyloxy-3(2H)-furanone* (**2bF**). 50.7 mg, 96% yield; pale yellow solid; mp 96.2−96.8 °C; $R_f$ = 0.58 (*n*-hexane/EtOAc = 1:2); IR (KBr): 2136, 1686, 1571 $cm^{-1}$; $^1H$ NMR (500 MHz, $CDCl_3$): $\delta$ 5.05 (d, *J* = 2.4 Hz, 2 H), 4.83 (s, 2 H), 2.70 (t, *J* = 2.4 Hz, 1 H); $^{13}C$ NMR (126 MHz, $CDCl_3$): $\delta$ 192.7, 181.3, 78.0, 76.0, 75.3, 57.9, 41.0; HRMS (ESI-TOF): *m*/*z* $[M + Na]^+$ calcd for $C_7H_5INaO_3$, 286.9176; found, 286.9173.

*4-Iodo-5-phenyloxy-3(2H)-furanone* (**2bG**). 52.3 mg, 87% yield; pale yellow solid; mp 152.5−154.0 °C (dec.); $R_f$ = 0.74 (*n*-hexane/EtOAc = 1:2); IR (KBr): 1687, 1569 $cm^{-1}$; $^1H$ NMR (500 MHz, $CDCl_3$): $\delta$ 7.47−7.43 (m, 2 H), 7.36−7.33 (m, 1 H), 7.23−7.21 (m, 2 H), 4.79 (s, 2 H); $^{13}C$ NMR (126 MHz, $CDCl_3$): $\delta$ 193.1, 180.8, 150.9, 129.9, 127.2, 120.6, 75.8, 42.1; HRMS (ESI-TOF): *m*/*z* $[M + Na]^+$ calcd for $C_{10}H_7INaO_3$, 324.9332; found, 324.9331.

*5-Benzyloxy-4-iodo-3(2H)-furanone* (**2bH**). 53.0 mg, 84% yield; pale yellow solid; mp 73.5−74.2 °C; $R_f$ = 0.60 (*n*-hexane/EtOAc = 1:2); IR (KBr): 1685, 1562 $cm^{-1}$; $^1H$ NMR (500 MHz, $CDCl_3$): $\delta$ 7.47−7.40 (m, 5 H), 5.48 (s, 2 H), 4.79 (s, 2 H); $^{13}C$ NMR (126 MHz, $CDCl_3$): $\delta$ 192.6, 181.7, 133.4, 129.3, 128.9, 128.2, 75.7, 72.3, 40.5; HRMS (ESI-TOF): *m*/*z* $[M + Na]^+$ calcd for $C_{11}H_9INaO_3$, 338.9513; found, 338.9501.

*5-(4-Bromobenzyl)oxy-4-iodo-3(2H)-furanone* (**2bI**). 71.2 mg, 90% yield; pale yellow solid; mp 143.3−143.9 °C; $R_f$ = 0.58 (*n*-hexane/EtOAc = 1:2); IR (KBr): 1687, 1568 $cm^{-1}$; $^1H$ NMR (500 MHz, $CDCl_3$): $\delta$ 7.57 (d, *J* = 8.4 Hz, 2 H), 7.30 (d, *J* = 8.4 Hz, 2 H), 5.42 (s, 2 H), 4.79 (s, 2 H); $^{13}C$ NMR (126 MHz, $CDCl_3$): $\delta$ 192.5, 181.5, 132.4, 132.2, 129.8, 123.6, 75.8, 71.4, 40.7; HRMS (ESI-TOF): *m*/*z* $[M + Na]^+$ calcd for $C_{11}H_8Br^{81}INaO_3$, 418.8574; found, 418.8575; calcd for $C_{11}H_8Br^{79}INaO_3$, 416.8594; found 416.8590.

**Large-Scale Procedure for the Synthesis of 5-Alkoxy-4-halo-3(2*H*)-furanones (2).** Equivalent amounts of DMAP and *N*-halosuccinimide were added to a solution of sulfonium salt **1** (5.0 mmol) in dry DMF (10 mL) at 0 °C. The reaction mixture was allowed to warm to room temperature and then stirred for 1 h. The mixture was treated with water and extracted with EtOAc. The organic extract was washed with an aqueous of 0.5 M $Na_2S_2O_3$, water (three times), and brine. The organic extract was dried over anhydrous $Na_2SO_4$ and concentrated under reduced pressure. Purification by flash column chromatography on silica gel (*n*-hexane/EtOAc = 1:1) gave the desired 5-alkoxy-4-halo-3(2*H*)-furanone **2**, as depicted in Scheme 4.



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**General Procedure for the Synthesis of 4-Aryl-5-ethoxy-3(2*H*)-furanones 3.** A Schlenk flask was charged with 5-ethoxy-4-iodo-3(2*H*)-furanone **2bA** (50.8 mg, 0.20 mmol), $Pd(OAc)_2$ (2.2 mg, 5 mol %), arylboronic acid (1.5 equiv), and CsF (91.2 mg, 3.0 equiv). To the Schlenk flask, degassed and dry THF (1.0 mL) was added via cannula, and the mixture was stirred at 40 °C for 21 h. The reaction mixture was treated with brine and extracted with EtOAc. The extract was dried over anhydrous $Na_2SO_4$ and concentrated under reduced pressure. Purification by flash column chromatography on silica gel (*n*-hexane/EtOAc = 1:1) gave the 4-aryl-5-ethoxy-3(2*H*)-furanone **3**.

*5-Ethoxy-4-phenyl-3(2H)-furanone (**3a**).* 33.2 mg, 81% yield; white solid; mp 118.5−119.3 °C; $R_f$ = 0.44 (*n*-hexane/EtOAc = 1:2); IR (KBr): 1667, 1588 $cm^{-1}$; $^1H$ NMR (500 MHz, $CDCl_3$): $\delta$ 7.87−7.85 (m, 2 H), 7.37−7.34 (m, 2 H), 7.21−7.18 (m, 1 H), 4.68 (s, 2 H), 4.59 (q, $J$ = 7.1 Hz, 2 H), 1.52 (t, $J$ = 7.1 Hz, 3 H); $^{13}C$ NMR (126 MHz, $CDCl_3$): $\delta$ 194.1, 180.6, 129.4, 128.2, 125.9 (2C), 93.9, 74.6, 66.6, 14.8; HRMS (ESI-TOF): $m/z$ $[M + Na]^+$ calcd for $C_{12}H_{12}NaO_3$, 227.0679; found, 227.0676.

*5-Ethoxy-4-(4-methylphenyl)-3(2H)-furanone (**3b**).* 38.1 mg, 87% yield; white solid; mp 127.5−127.7 °C; $R_f$ = 0.48 (*n*-hexane/EtOAc = 1:2); IR (KBr): 1681, 1588 $cm^{-1}$; $^1H$ NMR (500 MHz, $CDCl_3$): $\delta$ 7.74 (d, $J$ = 8.1 Hz, 2 H), 7.17 (d, $J$ = 8.1 Hz, 2 H), 4.67 (s, 2 H), 4.58 (q, $J$ = 7.1 Hz, 2 H), 2.33 (s, 3 H), 1.51 (t, $J$ = 7.1 Hz, 3 H); $^{13}C$ NMR (126 MHz, $CDCl_3$): $\delta$ 194.2, 180.5, 135.6, 128.9, 126.4, 125.9, 93.9, 74.5, 66.5, 21.2, 14.9; HRMS (ESI-TOF): $m/z$ $[M + Na]^+$ calcd for $C_{13}H_{14}NaO_3$, 241.0835; found, 241.0839.

*4-(4-Chlorophenyl)-5-ethoxy-3-(2H)-furanone (**3c**).* 38.9 mg, 81% yield; white solid; mp 109.0−109.3 °C; $R_f$ = 0.44 (*n*-hexane/EtOAc = 1:2); IR (KBr): 1675, 1579 $cm^{-1}$; $^1H$ NMR (500 MHz, $CDCl_3$): $\delta$ 7.84 (d, $J$ = 8.7 Hz, 2 H), 7.31 (d, $J$ = 8.7 Hz, 2 H), 4.68 (s, 2 H), 4.61 (q, $J$ = 7.1 Hz, 2 H), 1.33 (t, $J$ = 7.1 Hz, 3 H); $^{13}C$ NMR (126 MHz, $CDCl_3$): $\delta$ 193.9, 180.5, 131.2, 128.3, 128.0, 127.0, 93.0, 74.7, 66.9, 14.8; HRMS (ESI-TOF): $m/z$ $[M + Na]^+$ calcd for $C_{12}H_{11}ClNaO_3$, 261.0289; found, 261.0286.

**General Procedure for the Synthesis of 4-Alkynyl-5-ethoxy-3(2*H*)-furanones 4.** A Schlenk flask was charged with 5-ethoxy-4-iodo-3(2*H*)-furanone **2bA** (25.4 mg, 0.10 mmol), $Pd(PPh_3)_2Cl_2$ (2.1 mg, 3 mol %), and copper(I) iodide (2.0 mg, 10 mol %). The mixture of dry THF (0.5 mL), dry $Et_3N$ (0.5 mL), and the alkyne (2.0 equiv) was degassed using the freeze−pump−thaw technique (4 cycles) and added to the Schlenk flask via cannula. The mixture was stirred under reaction conditions depicted in Scheme 3, eq 2. The reaction mixture was treated with brine and extracted with EtOAc. The extract was dried over anhydrous $Na_2SO_4$ and concentrated under reduced pressure. Purification by flash column chromatography on silica gel (*n*-hexane/EtOAc = 1:1) gave the 4-alkynyl-5-ethoxy-3(2*H*)-furanone **4**.

*5-Ethoxy-4-trimethylsilylethynyl-3(2H)-furanone (**4a**).* 21.3 mg, 95% yield; white solid; mp 106.1−106.6 °C; $R_f$ = 0.48 (*n*-hexane/EtOAc = 1:2); IR (KBr): 2158, 1699, 1597 $cm^{-1}$; $^1H$ NMR (500 MHz, $CDCl_3$): $\delta$ 4.65 (q, $J$ = 7.1 Hz, 2 H), 4.63 (s, 2 H), 1.50 (t, $J$ = 7.1 Hz, 3 H), 0.21 (s, 9 H); $^{13}C$ NMR (126 MHz, $CDCl_3$): $\delta$ 193.8, 183.6, 100.6, 91.0, 81.4, 75.2, 67.9, 14.8, 0.0; HRMS (ESI-TOF): $m/z$ $[M + Na]^+$ calcd for $C_{11}H_{16}NaO_3Si$, 247.0761; found, 247.0759.

*5-Ethoxy-4-hex-1-ynyl-3(2H)-furanone (**4b**).* 17.3 mg, 83% yield; pale yellow solid; mp 39.1−39.4 °C; $R_f$ = 0.46 (*n*-hexane/EtOAc = 1:2); IR (KBr): 2363, 1686, 1578 $cm^{-1}$; $^1H$ NMR (500 MHz, $CDCl_3$): $\delta$ 4.62 (s, 2 H), 4.62 (q, $J$ = 7.1 Hz, 2 H), 2.40 (t, $J$ = 7.2 Hz, 2 H), 1.58−1.52 (m, 2 H), 1.48 (t, $J$ = 7.1 Hz, 3 H), 1.46−1.39 (m, 2 H), 0.91 (t, $J$ = 7.3 Hz, 3 H); $^{13}C$ NMR (126 MHz, $CDCl_3$): $\delta$ 194.5, 183.1, 96.2, 81.5, 75.0, 67.5, 66.1, 30.8, 22.0, 19.4, 14.8, 13.6; HRMS (ESI-TOF): $m/z$ $[M + Na]^+$ calcd for $C_{12}H_{16}NaO_3$, 231.0992; found, 231.0988.

*5-Ethoxy-4-phenylethynyl-3(2H)-furanone (**4c**).* 16.2 mg, 71% yield; pale yellow solid; mp 89.8−90.6 °C; $R_f$ = 0.40 (*n*-hexane/EtOAc = 1:2); IR (KBr): 2221, 1688, 1584 $cm^{-1}$; $^1H$ NMR (500 MHz, $CDCl_3$): $\delta$ 7.49−7.47 (m, 2 H), 7.31−7.28 (m, 3 H), 4.70 (s, 2 H), 4.66 (q, $J$ = 7.1 Hz, 2 H), 1.52 (t, $J$ = 7.1 Hz, 3 H); $^{13}C$ NMR (126 MHz, $CDCl_3$): $\delta$ 193.6, 183.0, 131.4, 128.1, 128.0, 123.3, 94.9, 81.2, 75.7, 75.4, 67.9, 14.8; HRMS (ESI-TOF): $m/z$ $[M + Na]^+$ calcd for $C_{14}H_{12}NaO_3$, 251.0679; found, 251.0672.

**Synthesis of 5-Ethoxy-4-vinyl-3(2*H*)-furanone 5.** A Schlenk flask was charged with 5-ethoxy-4-iodo-3(2*H*)-furanone **2bA** (25.4 mg, 0.10 mmol) and $Pd(PPh_3)_4$ (5.8 mg, 5 mol %). To the Schlenk flask was added degassed and dry toluene (1.0 mL), followed by tri(*n*-butyl)vinyltin (30 $\mu$L, 1.0 equiv), and the mixture was stirred at 80 °C for 6 h. The reaction mixture was treated with brine and extracted with EtOAc. The extract was dried over anhydrous $Na_2SO_4$ and concentrated under reduced pressure. Purification by flash column chromatography on silica gel (*n*-hexane/EtOAc = 1:1) gave the 5-ethoxy-4-vinyl-3(2*H*)-furanone **5** as a pale yellow solid (9.4 mg, 61% yield); mp 48.1−48.7 °C; $R_f$ = 0.48 (*n*-hexane/EtOAc = 1:2); IR (KBr): 1671, 1640, 1580 $cm^{-1}$; $^1H$ NMR (500 MHz, $CDCl_3$): $\delta$ 6.22 (dd, $J$ = 17.8, 11.6 Hz, 1 H), 5.84 (dd, $J$ = 17.8, 2.1 Hz, 1 H), 5.11 (dd, $J$ = 11.6, 2.1 Hz, 1 H), 4.57 (s, 2 H), 4.51 (q, $J$ = 7.1 Hz, 2 H), 1.47 (t, $J$ = 7.1 Hz, 3 H); $^{13}C$ NMR (126 MHz, $CDCl_3$): $\delta$ 193.9, 180.6, 121.9, 112.6, 93.6, 74.8, 66.4, 14.8; HRMS (ESI-TOF): $m/z$ $[M + Na]^+$ calcd for $C_8H_{10}NaO_3$, 177.0522; found, 177.0518.

## ■ ASSOCIATED CONTENT

### Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.7b00399.

$^1H$ NMR spectral data for an equimolar mixture of NIS and DMAP, the mixture of NXS with varying amounts of DMAP (0.2−1.0 equiv), and $^1H$ and $^{13}C$ NMR spectral data for **2**, **3**, **4**, and **5** (PDF)

## ■ AUTHOR INFORMATION


### Corresponding Author

*E-mail: tkawano@iwate-med.ac.jp.

### ORCID

Sho Inagaki: 0000-0002-7183-7030


### Notes

The authors declare no competing financial interest.

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