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Highly substituted benzo[*b*]furan synthesis through substituent migration†

Akihiro Kobayashi,[ab] Shinya Tabata[a] and Suguru Yoshida *[a]

An unusual benzofuran synthesis from 2,6-disubstituted phenols and alkynyl sulfoxides is disclosed. Various highly substituted benzofurans were synthesized *via* the charge-accelerated [3,3]-sigmatropic rearrangement and subsequent substituent migration. Multiaryl-substituted benzofurans and fully substituted benzofurans were prepared on the basis of the unique reaction mechanism.

The migration of substituents on aromatic rings has gained attention from organic chemists due to unique mechanisms as well as useful methods to prepare highly substituted arenes. In particular, the migration of alkyl groups on multisubstituted benzenes is known as the Jacobsen rearrangement and enables the synthesis of congested benzenes.[1] For example, 2,3,4,5-tetraalkylbenzenesulfonic acids were obtained from 1,2,4,5-tetraalkylbenzenes by sulfonylation in concentrated sulfonic acid through the rearrangement in carbocation intermediates **I** (Fig. 1A).[1c] Also, tetramethyl-substituted α-tetralone synthesis was achieved from 4-(2,3,5,6-tetramethylphenyl)butyric acid *via* the migration of methyl groups (Fig. 1B).[1d] Despite continuous studies for the rearrangement of cationic intermediates, it is still challenging to synthesize highly functionalized arenes through substituent migration in cationic intermediates.[2] Herein, we disclose an unexpected reaction through charge-accelerated [3,3]-sigmatropic rearrangement of sulfonium intermediates followed by substituent migration.

Recently, remarkable achievements in diverse transformations of sulfoxides through charge-accelerated [3,3]-sigmatropic rearrangement have enabled us to synthesize a wide variety of functionalized arenes owing to the intriguing reactivities of sulfonium intermediates.[3,4] A few examples of the [3,3]-sigmatropic rearrangement followed by migration of substituents realized the preparation of multisubstituted arenes in unusual manners. For instance, Maulide and coworkers developed a meta-selective rearrangement using *o*-substituted phenyl sulfoxides and ynamides catalyzed by Tf_2NH through charge-accelerated [3,3]-sigmatropic rearrangement and subsequent alkyl migration (Fig. 2A).[5a] On the other hand, benzofuran synthesis *via* dearomatized C–C formation of 2,6-difluorophenols was accomplished through the extended Pummerer reaction of sulfoxides facilitated by TFAA, where deprotonation took place to provide dearomatized intermediates without migration of an alkenyl or a fluoro group (Fig. 2B).[6] Considering these contrasting products from similar sulfonium intermediates, it is not easy to promote the rearrangement of *ortho*-substituent on aromatic rings. In contrast, we found a new method to prepare highly substituted benzo[*b*]furans from 2,6-substituted phenols with alkynyl sulfoxides in the presence of trifluoroacetic acid anhydride (TFAA) through substituted migration of cationic intermediate **II** (Fig. 1C).

Unusual substituent migration was found in the benzofuran synthesis from 2-substituted phenols with alkynyl sulfoxide **2a** facilitated by TFAA (Fig. 3A).[7] The reaction using 2-trifluoromethylphenol (**1a**) took place smoothly to afford 7-trifluoromethyl-substituted benzofuran **3a** *via* C–C formation at the sterically unhindered site (Fig. 3A, upper). To our surprise,

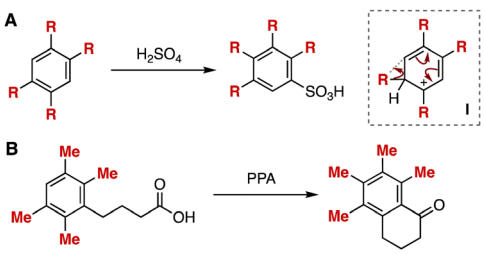

Fig. 1 (A) Alkyl migration in sulfonylation. (B) Methyl migration in cyclization. PPA = polyphosphoric acid.

[a] Department of Biological Science and Technology, Faculty of Advanced Engineering, Tokyo University of Science, 6-3-1 Niijuku, Katsushika-ku, Tokyo 125-8585, Japan. E-mail: s-yoshida@rs.tus.ac.jp

[b] Laboratory of Chemical Bioscience, Institute of Biomaterials and Bioengineering, Tokyo Medical and Dental University (TMDU), 2-3-10 Kanda-Surugadai, Chiyoda-ku, Tokyo 101-0062, Japan

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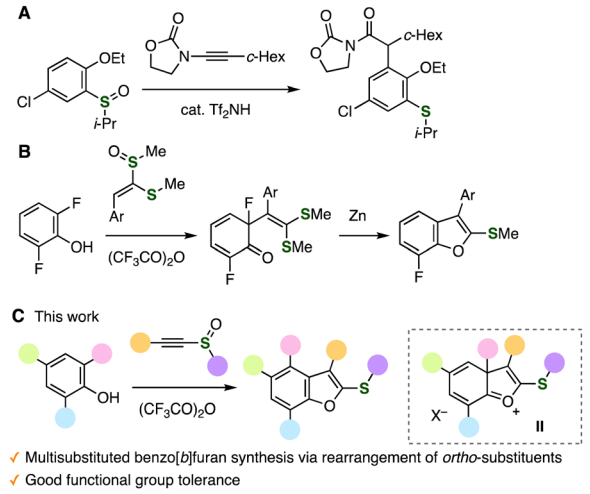

Fig. 2 (A) Maulide's study. (B) Yorimitsu's study. (C) This work.

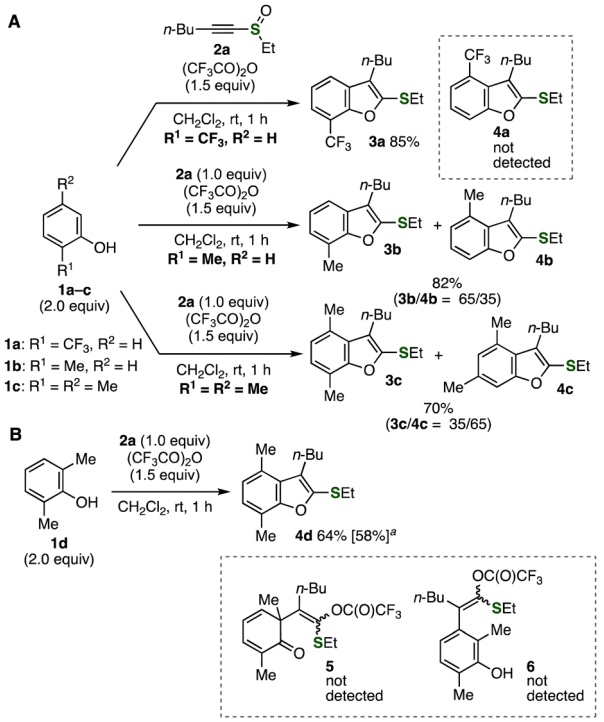

Fig. 3 (A) Benzofuran synthesis using phenols **1a–c**. (B) Benzofuran synthesis using 2,6-dimethylphenol (**1d**). [a] The reaction was conducted on a 1 mmol scale.

treatment of *o*-cresol (**1b**) with alkynyl sulfoxide **2a** in the presence of TFAA provided not only 7-methyl-substituted benzofuran **3b** but also 4-methyl-substituted benzofuran **4b** as an inseparable mixture (Fig. 3A, middle). When 2,5-dimethylphenol (**1c**) was treated with **2a** and TFAA, 4,6-dimethylsubstituted benzofuran **4c** was obtained as a major product along with 4,7-dimethylbenzofuran **3c** (Fig. 3A, lower). These results obviously showed that unusual substituent migration of cationic intermediates would be involved in the formation of benzofurans **4b** and **4c** although normal C–C formation also occurred to furnish benzofurans **3b** and **3c** by avoiding the steric repulsion at the *ortho*-substituents.

We succeeded in the selective synthesis of 4,7-dimethylsubstituted benzofuran **4d** (= **3c**) in good yield by the reaction of 2,6-dimethylphenol (**1d**) (Fig. 3B). In this reaction, C–C formation at the methyl-substituted carbon of phenol **1d** with alkynyl sulfoxide **2a**, migration of the methyl group to the neighboring site, and deprotonation would lead to the efficient formation of benzofuran **4d**. In contrast to the previous reports on the charge-accelerated [3,3]-sigmatropic rearrangement through aryloxysulfonium intermediates, dearomatized product **5** and 2,3,6-trisubstituted phenol **6** were not observed in the ^{1}H NMR analysis of the crude product after aqueous workup. Synthesis of benzofuran **4d** was also accomplished with good yield when the reaction was conducted on a 1 mmol scale.

A wide variety of tetra- or pentasubstituted benzofurans **4e–4l** were synthesized from 2,6-disubstituted phenols **1** (Fig. 4). Indeed, pentasubstituted benzofuran **4e** was successfully prepared in high yield without damaging the ester moiety. Efficient synthesis of diaryl ketones **4f** and **4g** was achieved using hydroxy-substituted diaryl ketones keeping ketone, methoxy, and bromo moieties unreacted. It is worth noting that treatment of 4-(pinacolatoboryl)-2,6-dimethylphenol (**1h**) with alkynyl sulfoxide **2a** and TFAA afforded pentasubstituted benzofuran **4h** having a transformable boryl group. A range of functional groups were migrated to the neighboring position. For example, we prepared 4,7-diphenylbenzofuran **4i** from 2,6-diphenylphenol (**1i**) and alkynyl sulfoxide **2a** in moderate yield through the migration of the phenyl group. Also, 4,7-dibromo-substituted benzofuran **4j** was synthesized from 2,6-dibromophenol (**1j**) *via* bromo migration. When using 2-ethyl-6-methylphenol (**1k**), an inseparable mixture of **4k** and **4k′** was obtained through the

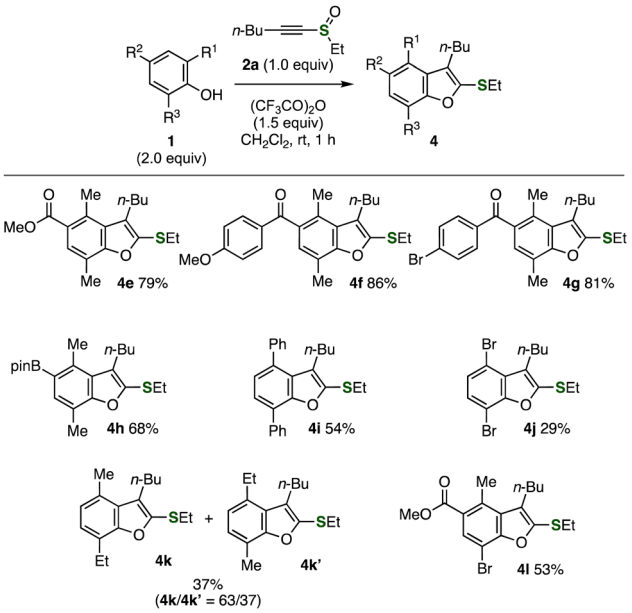

Fig. 4 Synthesis of benzofurans using various 2,6-disubstituted phenols. See the ESI† for details.

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migration of an ethyl or a methyl group, in which the formation of benzofuran **4k** *via* the migration of the methyl group was slightly favored.[1d] In addition, we succeeded in the selective synthesis of pentasubstituted benzofuran **4l** bearing ethylthio, butyl, methyl, methoxycarbonyl, and bromo groups through methyl migration.

The good functional group tolerance allowed us to synthesize diverse benzofurans **4** possessing a variety of functional groups from various alkynyl sulfoxides **2** (Fig. 5). For instance, we succeeded in the synthesis of aryl benzofuranyl sulfides **4m–o** bearing tolyl, 4-bromophenyl, and 2-thienyl groups. Efficient syntheses of benzyl sulfide **4p** and 6-chlorohexyl sulfide **4q** were accomplished in high yields through methyl migration without damaging benzyl and chloro groups. When using alkynyl sulfoxide having phenethyl, 2-(4-methylbenzoyloxy)ethyl, or 4-tolyl group, pentasubstituted benzofurans **4r–t** were prepared in good yields. Due to the good accessibility of divergent alkynyl sulfoxides from terminal alkynes and sulfur surrogates,[8] highly functionalized benzofurans will be synthesized from a variety of alkynyl sulfoxides with a broad range of 2,6-disubstituted phenols *via* the substituent migration.

To gain insight into the reaction mechanism, we then performed a competition experiment using phenols **1d** and **1i** using alkynyl sulfoxide **2a** (Fig. 6A). Indeed, treatment of an equimolar mixture of 2,6-dimethylphenol (**1d**) and 2,6-diphenylphenol (**1i**) with alkynyl sulfoxide **2a** in the presence of TFAA provided dimethyl-substituted benzofuran **4d** as a major product along with diphenyl-substituted benzofuran **4i** as a minor product. This result indicates that phenol **1d** having electron-donating alkyl groups showed higher reactivity than phenol **1i** having electron-withdrawing aryl groups. In addition, benzofurans 7 and 7′ bearing both methyl and phenyl groups were not observed, clearly

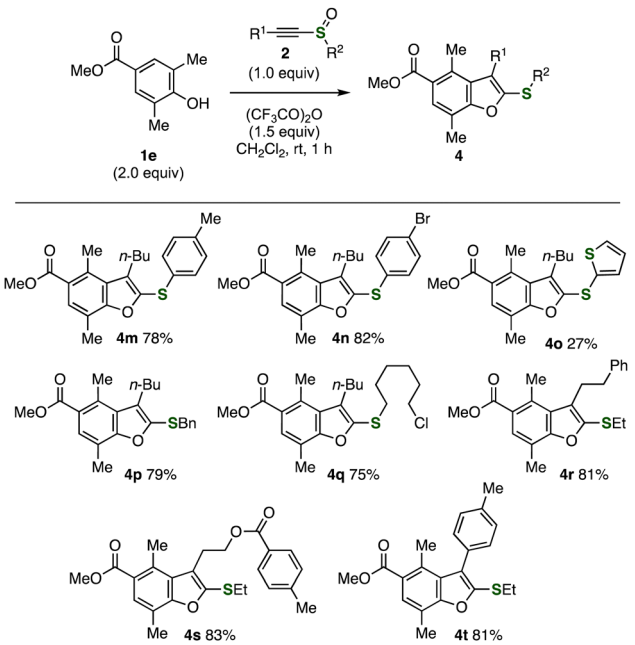

Fig. 5 Synthesis of benzofurans from various alkynyl sulfoxides and phenol **1e**.

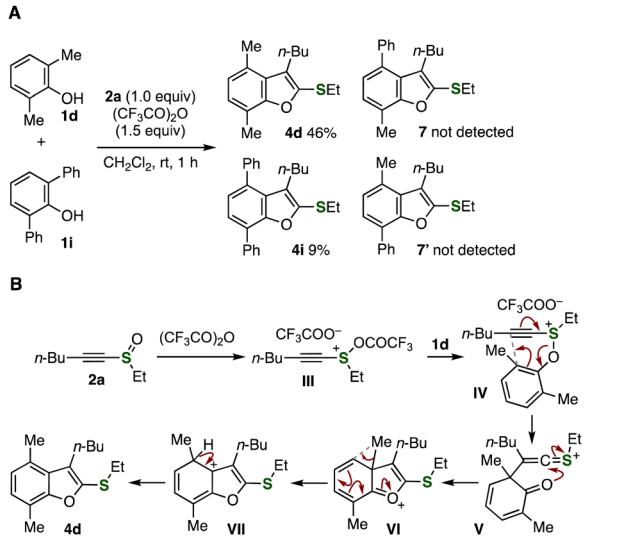

Fig. 6 (A) Benzofuran synthesis using a mixture of **1d** and **1i**. (B) Plausible reaction mechanism.

showing that the intramolecular migration step should be involved in the mechanism.

We propose a reaction mechanism through [3,3]-sigmatropic rearrangement followed by substituent migration (Fig. 6B). According to our previous report, electrophilic activation of alkynyl sulfoxide **2a** with TFAA first takes place to afford sulfonium (or sulfuran) intermediate **III**. Then, a substitution reaction of sulfonium intermediate **III** with phenol **1d** and charge-accelerated [3,3]-sigmatropic rearrangement of alkynyl sulfonium intermediate **IV** furnish dearomatized intermediate **V**.[9] The aromatized structure formed by ring closure, subsequent methyl migration, and deprotonation will provide 4,7-dimethyl-substituted benzofuran **4d**. In the ring-closing step, the C–O formation would be facilitated owing to the highly electron-deficient nature of thionium intermediate **V**, which prevents the migration of the alkynyl sulfoxide unit, leading to clear differences from the previous reports by Maulide or Yorimitsu.[5,6]

We showcased the synthetic utility of unusual migrative benzofuran formation by sequential cross-coupling reactions (Fig. 7A).[10] First, the selective synthesis of benzofuran **9** having an ethylthio group was accomplished from 2-bromo-6-phenylphenol (**1m**) and alkynyl sulfoxide **2a** *via* the migration of a phenyl group followed by Suzuki–Miyaura cross-coupling with arylboronic acid **8** at the bromo group efficiently without damaging the sulfide moiety.[11] Then, we succeeded in the further arylation of sulfide **9** with 4-tolylmagnesium bromide (**10**) in the presence of a catalytic amount of $IPrNiCl_2(PPh_3)$.[12] Since multisubstituted benzofuran **11** was synthesized from phenol **1m**, alkynyl sulfoxide **2a**, arylboronic acid **8**, and arylmagnesium bromide **10** in a modular synthetic manner, diverse highly substituted benzofurans would be prepared from easily available starting materials by the migrative benzofuran synthesis using 2,6-disubstituted phenols, organoboron, and Grignard reagents.

Inspired by the Jacobsen rearrangement in sulfonylation of 2,3,5,6-tetramethylbenzene,[1c] we accomplished the synthesis of

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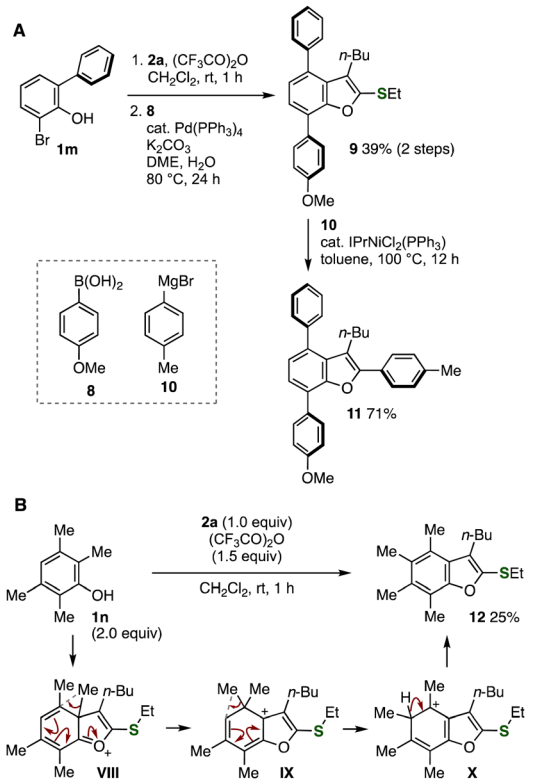

Fig. 7 (A) Synthesis of benzofuran **11**. (B) Synthesis of benzofuran **12** from 2,3,5,6-tetramethylphenol (**1n**).

fully substituted benzofuran **12** (Fig. 7B). Indeed, benzofuran **12** was successfully prepared by the treatment of 2,3,5,6-tetramethylphenol (**1n**) with alkynyl sulfoxide **2a** in the presence of TFAA. This result clearly demonstrates that the formation of fully substituted benzofuran **12** would be achieved *via* sequential migrations of methyl groups *via* intermediates **VIII** and **IX** followed by deprotonation. The unusual transformations *via* substituent migration of cationic intermediates would serve in synthesizing highly substituted arenes difficult to prepare by conventional methods.

In summary, we found an unusual substituent migration in the charge-accelerated [3,3]-sigmatropic rearrangement using 2,6-disubstituted phenols and alkynyl sulfoxides. A wide range of highly substituted benzofurans were successfully prepared through the [3,3]-sigmatropic rearrangement followed by the substituent migration. Since diverse benzofurans have served as significant bioactive compounds,[13] newly accessible multisubstituted benzofurans will be of great importance in pharmaceutical sciences and agrochemistry. Applications to the development of bioactive benzofurans, the synthesis of various heteroaromatics through similar reaction mechanisms, and theoretical studies with DFT calculations are ongoing in our laboratory.

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Conflicts of interest

There are no conflicts to declare.

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