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Synthesis of benzo[*b*]furans from alkynyl sulfoxides and phenols by the interrupted Pummerer reaction†

Akihiro Kobayashi,[ab] Tsubasa Matsuzawa,[b] Takamitsu Hosoya [b] and Suguru Yoshida *[a]

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The interrupted Pummerer reaction of alkynyl sulfoxides with phenols is disclosed. A wide range of benzo[*b*]furans were efficiently synthesized through unexplored electrophilic activation of the electron-deficient alkynyl sulfinyl group. Based on the good availability of alkynyl sulfoxides, we successfully prepared various functionalized benzo[*b*]furans from readily available alkynes, thiosulfonates, and phenols.

Introduction

Benzo[*b*]furan scaffolds are of great importance in a wide range of research fields including pharmaceutical sciences, natural product chemistry, and materials chemistry (Fig. 1A).[1] Various methods to synthesize benzofurans have been developed so far. For example, *O*-alkylation of salicylaldehyde derivatives with chloroacetic acid and subsequent cyclization affords a range of benzofurans.[2] Despite the significance of benzofurans, the synthesis of highly functionalized benzofurans is not easy by conventional methods due to limitations in the benzofuran skeleton construction. We herein describe a new method to prepare multisubstituted benzofurans from alkynyl sulfoxides and phenols *via* the interrupted Pummerer reaction.

The interrupted Pummerer reactions are emerging methods to synthesize highly functionalized organosulfur compounds from sulfoxides by the electrophilic activation of S=O bonds (Fig. 1B).[3] Recently, several unique transformations of a range of alkenyl and aryl sulfoxides with various nucleophiles have been achieved through the electrophilic activation of the sulfoxide moieties followed by smooth charge-accelerated [3,3]-sigmatropic rearrangement.[4,5] In contrast, interrupted Pummerer reactions of alkynyl sulfoxides have not been developed to the best of our knowledge, which may be due to the electron-deficient nature of the sulfoxide moiety by the electron-withdrawing sp-hybridized carbon. We conceived that the interrupted Pummerer reaction of alkynyl sulfoxides with phenols with the appropriate activators will allow us to synthesize a wide variety of functionalized benzofurans owing to the good availability of alkynyl sulfoxides and phenols (Fig. 1C).

Before examining the benzofuran synthesis, we evaluated the stability of alkynyl sulfurane intermediate **Ic** compared to alkenyl and alkyl sulfuranes **Ia** and **Ib** by the DFT calculation (Fig. 1D). The calculated energy differences between sulfoxides with trifluoroacetic anhydride (TFAA) and sulfuranes **Ia–Ic** showed that the electron-deficient alkynyl sulfurane **Ic** is unstable in comparison with alkyl and alkenyl sulfuranes **Ia** and **Ib**. These results clearly show that stability of sulfurane **Ic** was decreased by the significant electron-deficiency of alkynyl carbons. Comparing LUMO energies of **Ia–Ic** suggests higher electrophilicity of alkynyl sulfurane **Ic** than that of alkyl and alkenyl sulfuranes **Ia** and **Ib**.

Results and discussion

After screening the reaction conditions, we established the synthetic method of benzofuran **3a** from phenol (**1a**) and alkynyl sulfoxide **2a** through electrophilic sulfoxide activation (Table 1). While benzofuran **3a** was not obtained when acetic anhydride was used as an activator (entry 1), we found that treating a mixture of phenol (**1a**) and alkynyl sulfoxide **2a** with triflic anhydride (Tf_2O) afforded 3-butyl-2-(ethylthio)benzo[*b*]furan (**3a**) in moderate yield (entry 2). The yield was improved by the addition of 2,6-di(*tert*-butyl)pyridine as a base (entry 3).[6] We accomplished the synthesis of benzofuran **3a** from **1a** and **2a** in dichloromethane with TFAA in excellent yield (entry 4).[7] Benzofuran **3a** was also prepared in 1 mmol scale without decreasing the yield, showing the good scalability of the protocol (entry 5). Although we failed the synthesis of benzofuran **3a** when using 2,6-di(*tert*-butyl)pyridine or triethylamine as an additive (entries 6 and 7), benzofuran **3a** was also obtained

[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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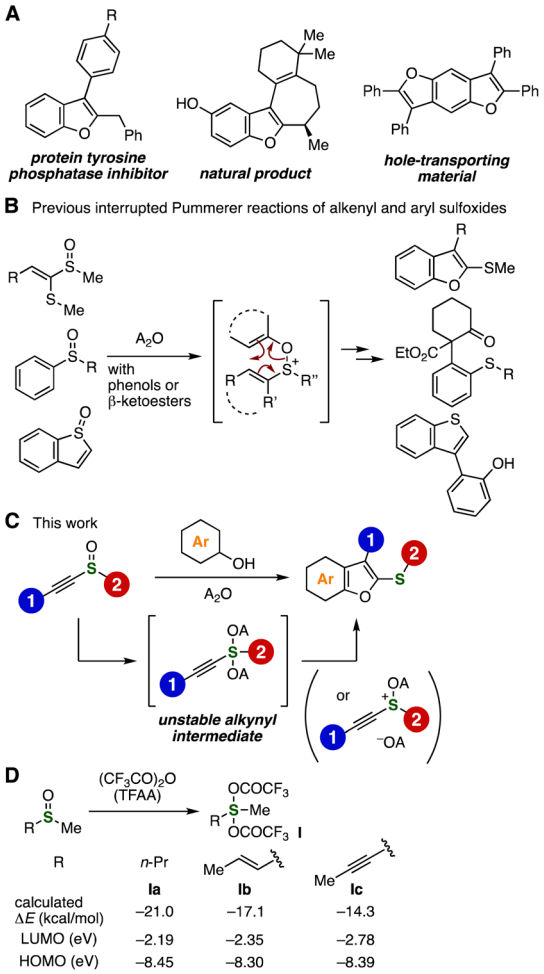
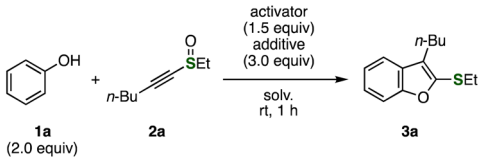


Fig. 1 Backgrounds and an abstract of this study. (A) Significant benzofurans. (B) Interrupted Pummerer reactions. (C) This work. (D) DFT calculations of sulfuranes **Ia–Ic**. $\Delta E = E$(sulfuranes) $- E$(sulfoxides) $- E$(TFAA). See ESI† for details.

Table 1 Screening of the reaction conditions



Entry	Activator	Additive	Solv.	Yield[a] (%)
1	Ac_2O	None	CH_2Cl_2	0
2	Tf_2O	None	CH_2Cl_2	45
3	Tf_2O	2,6-(*t*-Bu)$_2$pyridine	CH_2Cl_2	81
4	TFAA	None	CH_2Cl_2	97 (94)[b]
5	TFAA	None	CH_2Cl_2	95[c]
6	TFAA	2,6-(*t*-Bu)$_2$pyridine	CH_2Cl_2	0
7	TFAA	NEt_3	CH_2Cl_2	0
8	TFAA	Na_2CO_3	CH_2Cl_2	89
9	TFAA	None	MeCN	67
10	TFAA	None	THF	0
11	TFAA	None	Toluene	85
12	TFAA	None	$PhCF_3$	91
13	CF_3CO_2H	None	CH_2Cl_2	0

[a] ^{1}H NMR yield. [b] Isolated yield (0.1 mmol scale). [c] Isolated yield (1 mmol scale).

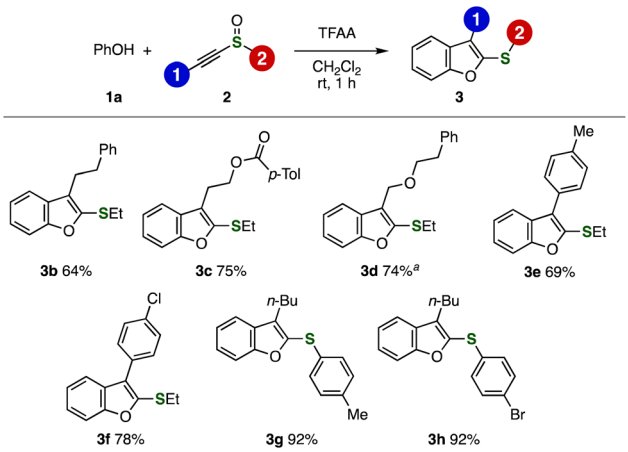


Fig. 2 Syntheses of benzofurans **3** using various alkynyl sulfoxides **2**. See the ESI† for details. [a]The reaction was performed with Tf_2O and 2,6-di(*tert*-butyl)pyridine.

in the presence of sodium carbonate (entry 8). Among solvents examined (entries 4 and 9–12), dichloromethane, toluene, and α,α,α-trifluorotoluene were effective for benzofuran synthesis (entries 4, 11, and 12). Trifluoroacetic acid did not activate sulfoxide **2a** (entry 13).

With optimized conditions in hand, a wide range of 2-sulfanylbenzofurans **3** were synthesized from phenol (**1a**) and various alkynyl sulfoxides **2** (Fig. 2). For example, phenethyl-substituted benzofuran **3b** was synthesized in good yield. It is worthy to note that an ester moiety was tolerated under the conditions, providing benzofuran **3c** in high yield. We succeeded in the synthesis of ether-tethered benzofuran **3d** by electrophilic activation with Tf_2O in the presence of 2,6-di(*tert*-butyl)pyridine in good yield, where decomposition took place when the reaction was conducted with TFAA. Benzofurans **3e** and **3f** having aryl groups at 3-position were prepared efficiently without damaging 4-tolyl and 4-chlorophenyl groups. Also, alkynyl aryl sulfoxides participated to the benzofuran synthesis affording **3g** and **3h** bearing 4-tolylthio and 4-bromophenylthio groups in high yields. Since a wide variety of alkynyl sulfoxides were easily available from terminal alkynes or alkynylsilanes,[8] the broad scope of the benzofuran synthesis is a great advantage over previous reports.[4]

Diverse functionalized benzofurans were successfully synthesized from alkynyl sulfoxide **2a** and a broad variety of phenols (Fig. 3). Indeed, phenols having methyl, methoxy, bromo, chloro, and methoxycarbonyl groups served in the benzofuran synthesis with alkynyl sulfoxide **2a** in moderate to high yields keeping the functional groups unreacted. Furthermore, the reaction of 2-trimethylsilyl-3-triflyloxyphenol (**1h**) with alkynyl sulfoxide **2a** efficiently proceeded to furnish benzofuran **3o** leaving butyl, ethylthio, trimethylsilyl, and

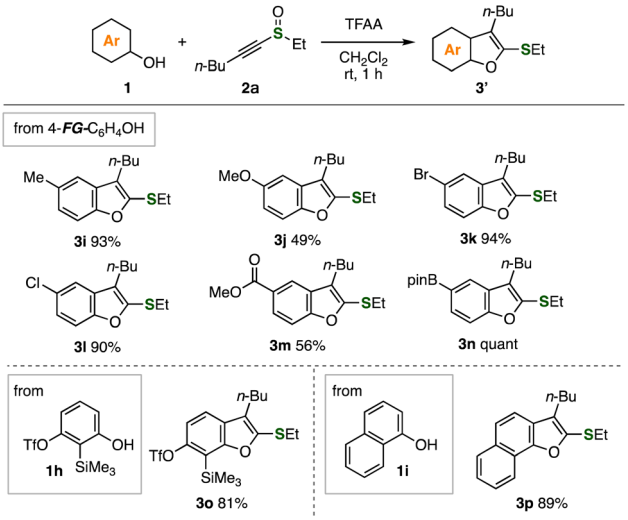


Fig. 3 Syntheses of benzofurans **3** using various phenols. See the ESI† for details.

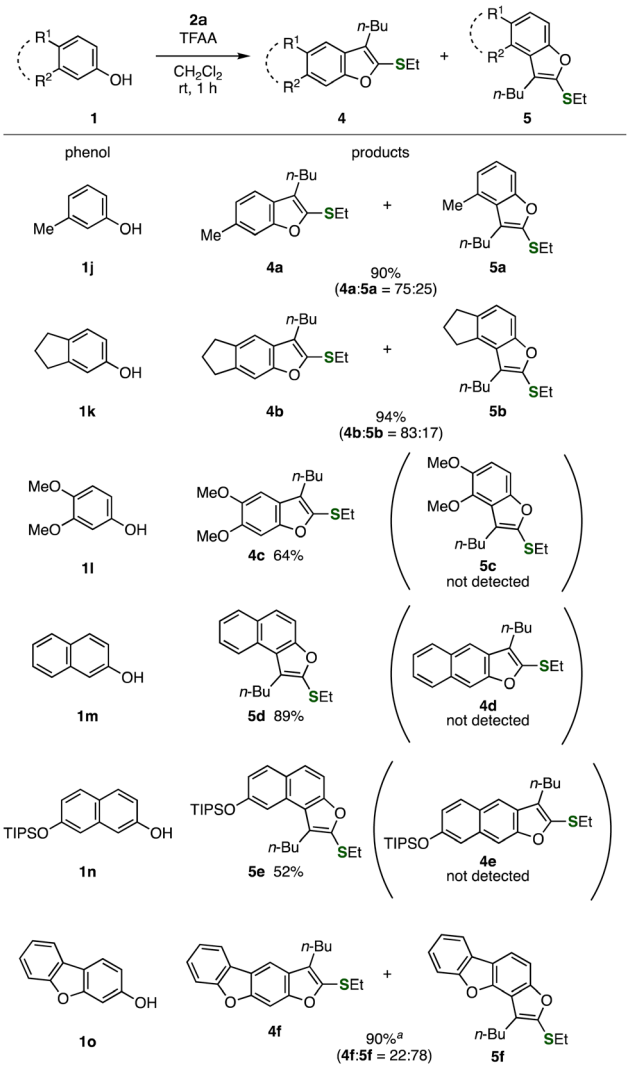


Fig. 4 Syntheses of benzofurans **4** and **5** using various phenols. See the ESI† for details. [a] ^{1}H NMR yield. Authentic samples (**4f** 7%; **5f** 65%) were isolated respectively.

triflyloxy groups untouched. In addition, naphthofuran **3p** was synthesis from 1-naphthol (**1i**) in good yield.

We then examined the regioselectivity in the benzofuran synthesis (Fig. 4). When the benzofuran synthesis was performed using *m*-cresol, 6-methyl-substituted benzofuran **4a** was majorly obtained along with 4-methylbenzofuran **5a** with moderate regioselectivity, clearly showing that the C–C bond formation at the unhindered site was favorable. Benzofuran **4b** was also synthesized as a major product with good regioselectivity when using 5-hydroxyindane (**1k**). Of note, we succeeded in the preparation of benzofuran **4c** as a sole product, in which the C–C bond formation at the vacant position took place selectively and regioisomer **5c** was not observed. In contrast, naphthols **1m** and **1n** reacted with alkynyl sulfoxide **2a** at the hindered site affording naphthofurans **5d** and **5e** selectively without forming regioisomers **4d** and **4e**, where cyclization took place at more electron-rich carbons.[9] Moreover, we achieved the synthesis of benzofuran-fused benzofurans **4f** and **5f** in good yields, in which C–C bond formation at 4-position occurred primarily in moderate selectivity.

To clarify the reaction mechanism of the benzofuran formation, we conducted control experiments (Fig. 5A). In order to examine the stability of intermediates generated *in situ* by the electrophilic activation of sulfoxides, we performed the addition of aqueous sodium bicarbonate or phenol (**1a**) after the prior activation of alkynyl sulfoxide **2a** with TFAA in dichloromethane for 1 h at room temperature (Fig. 5A). As a result, sulfoxide **2a** or benzofuran **3a** was respectively obtained through the hydrolysis or the reaction with phenol (**1a**) in slightly decreased yields, suggesting that side reactions such as the Pummerer rearrangement did not take place smoothly even in the absence of phenols.[10]

A plausible reaction mechanism is shown in Fig. 5B. First, the formation of sulfurane intermediates **I′** from alkynyl sulfoxides **2** by the electrophilic activation with TFAA followed by the nucleophilic substitution with **1a** would afford intermediates **II**.[3] Because side-products by the C–C bond formation of activated alkynyl sulfoxides **I′** with **1a** at *para*-position were not observed,[11] smooth S–O bond formation providing intermediates **II** would take place as previously reported interrupted Pummerer reactions.[4] Then, the sigmatropic rearrangement of alkynyl sulfuranes **II** and subsequent deprotonation lead to benzofurans **3**.[12]

Then, we showcased the benefits of the benzofuran synthesis from alkynyl sulfoxides and phenols (Fig. 6). A variety of benzofurans **3q–3s** were efficiently synthesized from alkyl halides **6a–6c**, sodium thiosulfonate, 1-hexyne, and phenol since sodium thiosulfonate worked as an "$^+$S$^-$" equivalent (Fig. 6A). Indeed, the preparation of alkynyl sulfides by *S*-alkylation and *S*-alkynylation followed by *S*-oxidation and the benzofuran formation allowed us to access easily functionalized benzofurans by the four-step four-component coupling protocols in a modular synthetic manner.

The good transformability of the sulfanyl group served in synthesizing a wide range of benzofurans (Fig. 6B). For example,

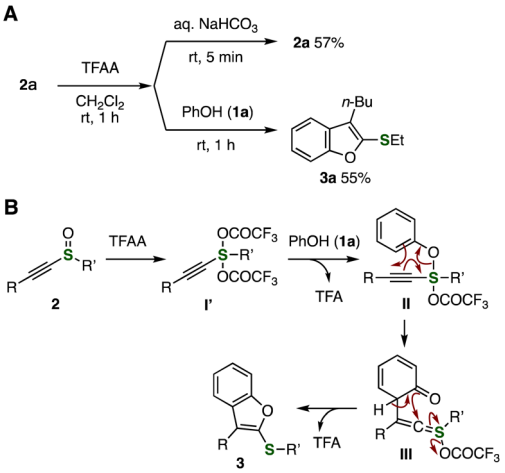


Fig. 5 Control experiments and reaction mechanism. (A) The reaction of alkynyl sulfoxide **2a** with TFAA. (B) Plausible reaction mechanism. See the ESI† for details.

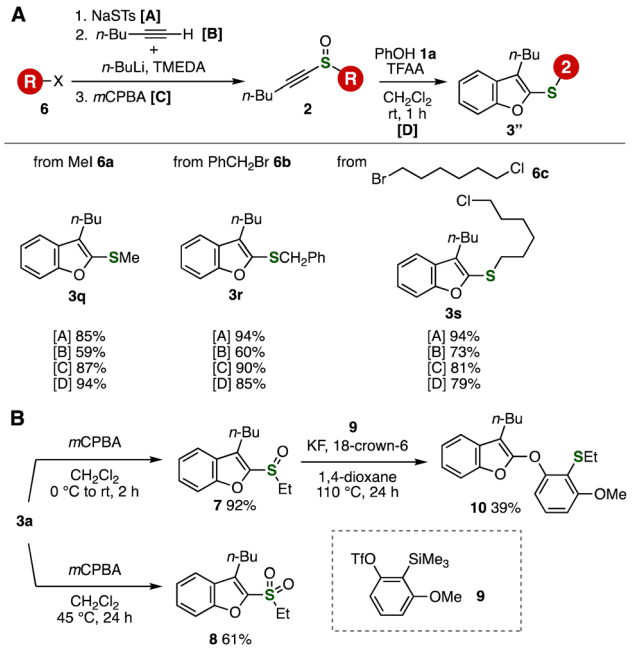


Fig. 6 (A) Benzofuran synthesis from alkyl halides. (B) Synthesis of organosulfur compounds from **3a**.

we succeeded in the preparation of sulfoxide **7** and sulfone **8** by *S*-oxidation of **3a**. Since a variety of transformations of the sulfinyl groups can be accomplished, the benzofuran formation and following *S*-oxidation and subsequent transformations such as aryne reactions[13,14] realize the synthesis of highly functionalized benzofurans. Indeed, the migratory oxythiolation of 3-methoxybenzyne from *o*-silylaryl triflate **9** and sulfoxide **7** with potassium fluoride and 18-crown-6 in 1,4-dioxane at 110 °C took place smoothly to provide highly functionalized benzofuran **10** *via* the C–S and two C–O bond formations, in which the migration of the 3-butylbenzofuran-2-yl group selectively proceeded in the C–O bond formation.[14]

Conclusions

In conclusion, we found a new method to synthesize benzo[*b*]furans from alkynyl sulfoxides and phenols by the electrophilic activation of the electron-deficient alkynyl sulfinyl moiety. Owing to the ready availability of alkynyl sulfoxides, the efficient synthetic method enabled us to prepare a wide range of functionalized benzofurans having sulfanyl groups. Since organosulfur substituents are easily transformed into various functional groups, the benzofuran synthesis will serve in developing diverse bioactive molecules. Further studies such as theoretical calculations are ongoing in our laboratory.

Conflicts of interest

There are no conflicts to declare.

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