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Facile Synthesis of Multisubstituted Benzo[*b*]furans via 2,3-Disubstituted 6,7-Furanobenzynes Generated from *ortho*-Iodoaryl Triflate-type Precursors

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Facile Synthesis of Multisubstituted Benzo[*b*]furans via 2,3-Disubstituted 6,7-Furanobenzynes Generated from *ortho*-Iodoaryl Triflate-type Precursors

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2,3-Disubstituted 6,7-furanobenzynes were efficiently generated from *ortho*-iodoaryl triflate-type precursors using a silylmethyl Grignard reagent as the activator. The reactions between 6,7-furanobenzynes and unsymmetrical arynophiles proceeded in a highly regioselective manner. Since a variety of precursors were easily synthesizable from readily available 2,3-disubstituted 6-hydroxybenzofurans, this method enabled facile synthesis of a wide range of multisubstituted benzofurans, including π-extended molecules.

Keywords: Aryne | Benzofuran | Grignard Reagent

Benzo[*b*]furan is a heterocycle often contained in a wide range of important molecules, including bioactive natural products, drugs, and hole-transporting materials (Figure 1).[1–4] In addition to the classical method for benzofuran synthesis based on cyclocondensation, recent approaches such as transition-metal catalyzed reactions and extended Pummerer reactions have enabled various benzofuran derivatives accessible.[5,6] However, transformation of simple benzofurans to more complex ones largely depends on limited classical reactions such as Friedel–Crafts reaction.[1] Therefore, a novel method that allows for diversification of simple benzofurans to multisubstituted derivatives, including those fused with another ring system, is required.

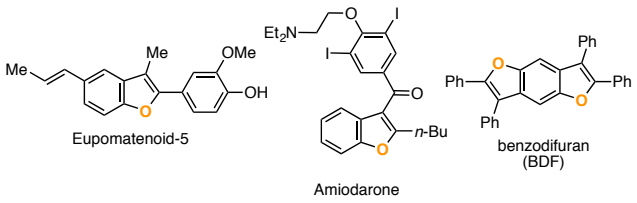


Figure 1. Various benzofuran derivatives.

Arynes are highly reactive intermediates useful for preparing diverse aromatic compounds.[7–16] Pioneering works on a furanobenzyne, which is a benzyne fused with a furan ring, have demonstrated the potential of this species as a synthetic intermediate of diverse benzofurans. For example, Brown and Buszek reported that furano[4,5-*c*]benzyne (**Ia**, 6,7-furanobenzyne) could be generated from 6,7-dibromobenzofuran by the treatment with *n*-butyllithium and used it as a dienophile in the Diels–Alder reactions (Figure 2A).[11a] Recently, Garg and coworkers reported a fluoride-mediated generation method of 4,5-furanobenzyne (**Ib**) from *ortho*-silylaryl triflate-type precursor (Figure 2B).[11b] These notable studies clearly demonstrated that furanobenzynes are useful intermediates for preparing benzofuran derivatives, which are difficult to synthesize by conventional methods. However, probably due to the unavailability of complex substrates, only simple furanobenzyne precursors, particularly 2,3-unsubstituted ones, have been reported, largely limiting the range of synthesizable benzofurans. Here we report an efficient generation method of 2,3-disubstituted 6,7-furanobenzynes from easily preparable *ortho*-iodoaryl triflate-type precursors and their application to the synthesis of multisubstituted benzofurans (Figure 2C).

We have recently developed an efficient method for generating arynes such as thiazolobenzynes and thienobenzynes from *ortho*-iodoaryl triflate-type precursors by treating them with a silylmethyl Grignard reagent.[10e,g] Based on these studies, we assumed that 6,7-furanobenzynes could be generated from *ortho*-iodoaryl triflate-type precursors **1**. We also assumed that, in combination with reported methods,[5,6] a variety of 2,3-substituted precursors could be prepared easily from mono-protected resorcinol in four steps; e.g., benzofuran formation, deprotection, iodination, and triflylation (Figure 2C).

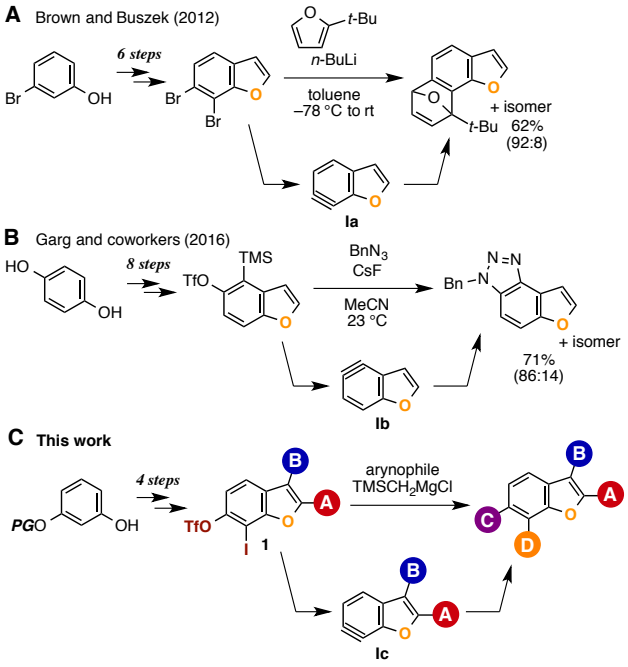
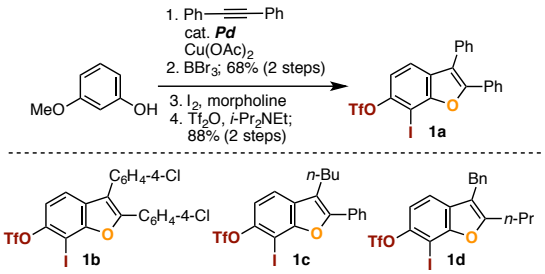


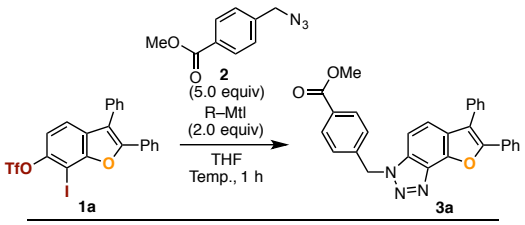
Figure 2. Synthesis of benzofuran derivatives via furanobenzynes. (A) Transformation via 6,7-furanobenzyne (**Ia**) generated from 6,7-dibromobenzofuran reported by Brown and Buszek.[11a] (B) Transformation via 4,5-furanobenzyne (**Ib**) generated from *ortho*-silylaryl triflate-type precursor reported by Garg and coworkers.[11b] (C) Transformation via 2,3-disubstituted 6,7-furanobenzyne **Ic** generated from *ortho*-iodoaryl triflate-type precursors **1**.



Scheme 1. Synthesis of 2,3-substituted 6,7-furanobenzyne precursors **1**.

Based on this idea, we firstly prepared 2,3-diphenyl-6-methoxybenzo[*b*]furan from 3-methoxyphenol and diphenylacetylene based on the palladium-catalyzed oxidative annulation method reported by Sahoo and coworkers,[5j] and derived it to *ortho*-iodoaryl triflate-type 6,7-furanobenzyne precursor **1a** in three steps; demethylation, regioselective iodination, and triflylation (Scheme 1).[17] Similarly, three other 2,3-disubstituted 7-iodo-6-triflyloxybenzo[*b*]furans **1b–d** were prepared.

Table 1. Optimization of the reaction conditions

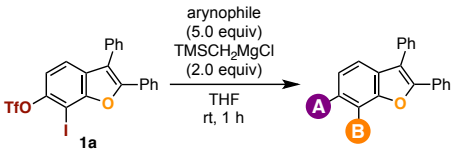


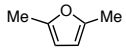
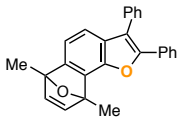
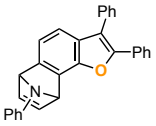
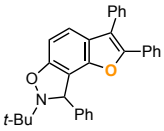
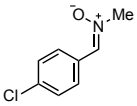
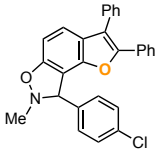
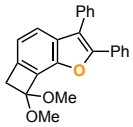
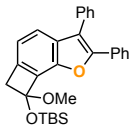
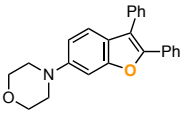
Entry	R–MtI	Temp. (°C)	Yield (%)[a]
1	*n*-BuLi	–78	25
2	*i*-PrMgCl·LiCl	–78	41
3	$TMSCH_2MgCl$	–78	63[b]
4	$TMSCH_2MgCl$	–40	74
5	$TMSCH_2MgCl$	0	81
6	$TMSCH_2MgCl$	rt	84[b]

[a]Yields based on ^{1}H NMR analyses, unless otherwise noted. [b]Isolated yield.

The reaction conditions that allowed for the efficient generation of 6,7-furanobenzyne were screened using *ortho*-iodoaryl triflate **1a** and methyl 4-(azidomethyl)benzoate (**2**) as an arynophile (Table 1). Although the desired cycloadduct **3a** was obtained only in low yields by treatment of the mixture of **1a** and **2** (5.0 equiv) in THF with *n*-butyllithium[12a] or isopropylmagnesium chloride–lithium chloride complex[12b] at −78 °C (entries 1 and 2), treatment with (trimethylsilyl)methylmagnesium chloride afforded **3a** in a better yield (entry 3). These results were similar to those observed in our previous studies on the generation of thiazolobenzynes,[10e] thienobenzynes,[10g] 3-triflyoxyarynes,[10b,f] and 3-(propargyloxy)benzyne,[10a] in which the less nucleophilic silylmethyl Grignard reagent most effectively triggered the generation of arynes from *ortho*-iodoaryl triflates via iodine–magnesium exchange reaction. Further improvement of the yield of **3a** was achieved by performing the reaction at a higher temperature (entries 4–6). In particular, the reaction at room temperature afforded **3a** in the highest yield (entry 6). Notably, the regioisomer of **3a** was not obtained from the reaction under these conditions, indicating that cycloaddition between 6,7-furanobenzyne and azide **2** proceeded selectively.

Table 2. Cycloadditions of 6,7-furanobenzyne

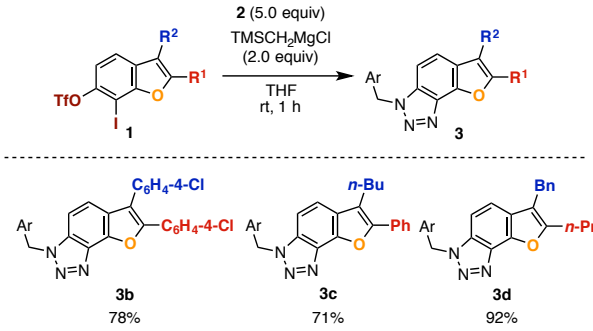


Entry	Arynophile		Product		Yield (%)
1		**4**		**5**	87
2		**6**		**7**	82
3		**8**		**9**	78
4		**10**		**11**	89
5		**12**		**13**	80
6		**14**		**15**	86
7		**16**		**17**	88

The optimized conditions (Table 1, entry 6) were successfully applied to the syntheses of a variety of multisubstituted benzofurans via the 6,7-furanobenzyne intermediate generated from the precursor **1a** (Table 2). 6,7-Ring-fused 2,3-diphenybenzo[*b*]furans **5** and **7** were obtained in high yields via Diels–Alder reaction of 6,7-furanobenzyne with 2,5-dimethylfuran (**4**) or *N*-phenylpyrrole (**6**), respectively (entries 1 and 2). Cycloadditions with nitrones **8**, **10** and ketene acetals **12**, **14** successfully provided oxazole-fused benzofurans **9**, **11** and cyclobutene-fused benzofurans **13**, **15**, respectively, as a single isomer (entries 3–6). Nucleophilic addition of secondary amine **16** to 6,7-furanobenzyne also took place efficiently in a regioselective

manner to afford 6-morpholinobenzofuran **17** as a sole product (entry 7). This high regioselectivity is worthy to note because nucleophilic amination to 3,4-cyclobutabenzyne,[13] pyrrolobenzyne (indolyne),[14] thiazolobenzyne,[10e] and thienobenzyne,[10g] which are 4- or 5-membered-ring-fused benzyne species similar to furanobenzyne, were reported to furnish a mixture of regioisomers with moderate to good selectivities.

The method was successfully applied to the generation of various 2,3-disubstituted 6,7-furanobenzynes from precursors **1b–d** (Scheme 2). For example, 2,3-di(4-chlorophenyl)-6,7-furanobenzyne was efficiently generated from **1b** under the optimized conditions, which reacted with azide **2** to afford 1,2,3-triazole-fused benzofuran **3b** in high yield without affecting the chloro group. 2-Phenyl-3-*n*-butyl- and 2-*n*-propyl-3-benzyl-substituted benzofurans, **3c** and **3d**, were also obtained from the corresponding 6,7-furanobenzyne precursors **1c** or **1d**, respectively. In every case, formation of regioisomer was not observed as contrasted with the case of the reactions of 2,3-disubstituted 6,7-thienobenzynes with azide **2**, which generally afforded a small amount of regioisomer.[10g]



Scheme 2. Cycloadditions of various 2,3-disubstituted 6,7-furanobenzynes with azide **2**. Ar = 4-(MeO$_2$C)C$_6$H$_4$-.

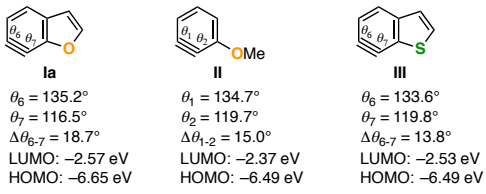
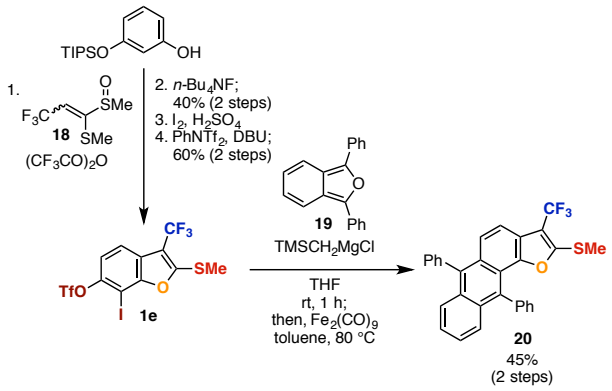


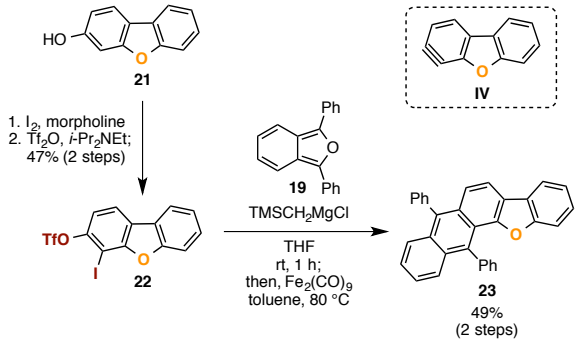
Figure 3. Optimized structures of 6,7-furanobenzyne (**Ia**), 3-methoxybenzyne (**II**), and 6,7-thienobenzyne (**III**) using a DFT method (B3LYP/6-311+G(d,p)).

To gain an insight into the remarkable regioselectivity observed in the reactions of 6,7-furanobenzynes, we optimized the structures of 6,7-furanobenzyne (**Ia**), 3-methoxybenzyne (**II**), and 6,7-thienobenzyne (**III**) based on density functional theory (DFT) at the B3LYP/6-311+G(d,p) level of theory using the Spartan '14 program (Figure 3).[17] The optimized geometry structure of **Ia** agreed well with that previously reported by Paton, Houk, Garg, and coworkers in the same manner as our previous studies on thiazolobenzynes and thienobenzynes.[15] The difference in the calculated values of internal angles at the aryne carbons ($\Delta\theta_{a\text{-}b} = \theta_a - \theta_b$) in the optimized structure of **Ia** is larger than those for **II** and **III**, indicating that the structure of **Ia** is more distorted than **II** and **III**, which resulted in the high regioselectivity. In addition to the high electronegativity of oxygen atom, the strain induced by the fused furan ring must have contributed to enhance the distortion of **Ia**.[8g,10e,g,11,14–17] Furthermore, the calculated LUMO level of **Ia** is lower than that of **II** and **III**, which indicated the higher electrophilicity of furanobenzyne.

Furanobenzyne intermediates were useful in synthesizing novel π-extended molecules containing a 2,3-substituted benzofuran structure as demonstrated in the short-step synthesis of furanoanthracene **20** and benzofuran-fused anthracene **23** (Schemes 3 and 4). Thus, 2-methylthio-3-trifluoromethyl-6,7-furanobenzyne precursor **1e** was easily prepared from 3-(triisopropylsilyloxy)phenol and ketene dithioacetal monoxide **18** based on Yorimitsu benzofuran synthesis,[6] followed by protodesilylation, regioselective iodination, and triflylation (Scheme 3). Diels–Alder reaction between 2-methylthio-3-trifluoromethyl-6,7-furanobenzyne, generated from **1e**, and 1,3-diphenylisobenzofuran (**19**) and subsequent deoxygenative aromatization[18] using $Fe_2(CO)_9$ furnished furanoanthracene **20** bearing methylthio and trifluoromethyl groups. Dibenzofuran-type aryne **IV**[19] was also generated from the corresponding *ortho*-iodoaryl triflate-type precursor **22**, which was prepared from 3-dibenzofuranol (**21**) through regioselective iodination and triflylation (Scheme 4). The reaction of aryne with **19**, followed by aromatization afforded pentacyclic compound **23**.



Scheme 3. Synthesis of furanoanthracene **20** via 6,7-furanobenzyne.



Scheme 4. Synthesis of benzofuran-fused anthracene **23** via dibenzofuran-type aryne.

In summary, we have developed an efficient method for generating 2,3-disubstituted 6,7-furanobenzynes from *ortho*-iodoaryl triflate-type precursors. Since various precursors are easily available from phenols, transformations via 6,7-furanobenzynes allow for the synthesis of a diverse range of

multisubstituted benzofuran derivatives, including π-extended molecules. Further studies to expand the scope of the method, such as generation and transformations of 4,5- and 5,6-furanobenzynes, detailed theoretical study, and synthesis of practical π-extended molecules are now in progress.

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Supporting Information for experimental procedures and characterization of new compounds are available electronically on J-STAGE.

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