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Facile Diversification of Simple Benzo[*b*]thiophenes via Thienobenzyne Intermediates

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Thienobenzynes, which are thiophene-fused novel benzyne species, are efficiently generated via an iodine–magnesium exchange reaction of *ortho*-iodoaryl triflate-type precursors using a silylmethyl Grignard reagent as the activator. The method has allowed for facile preparation of a diverse range of multisubstituted benzothiophenes from readily available simple benzothiophenes.

Keywords: Aryne | Benzo[*b*]thiophene | Grignard Reagent

Benzo[*b*]thiophene derivatives have important applications in various disciplines, including pharmaceutical, agrochemical, and materials sciences (Figure 1).[1–3] Various efficient synthetic methods for benzothiophenes have been developed, such as electrophile- or radical-mediated cyclization and transition metal-catalyzed annulation approaches.[4,5] However, these methods are not always applicable to the synthesis of more complex multisubstituted benzothiophenes, including those fused with another ring system, for which an alternative approach is required.

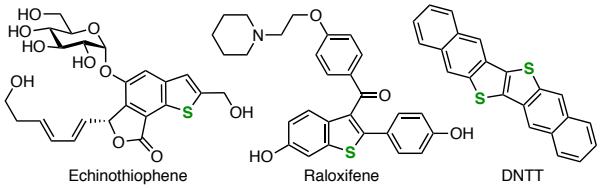


Figure 1. Various benzothiophene derivatives.

Recent advances in aryne chemistry have offered easy access to a wide range of complex aromatic compounds.[6–9] We assumed that a thienobenzyne, which is an unused benzyne species fused with a thiophene ring, would be a convenient intermediate for preparing diverse benzothiophene derivatives. This idea was based on our recent achievements in aryne chemistry.[8,9] In particular, we recently demonstrated that multisubstituted benzothiazoles are readily available via thiazolobenzyne intermediates, thiazole-fused benzyne species.[9e] Thiazolobenzynes were efficiently generated from easily synthesized *ortho*-iodoaryl triflate-type precursors[10] by treatment with a trimethylsilylmethyl Grignard reagent, which was used to trigger an iodine–magnesium exchange reaction.[9] We envisioned that a similar strategy, using thienobenzynes instead of thiazolobenzynes, would provide easy access to multisubstituted benzothiophenes (Figure 2). We assumed that a variety of *ortho*-iodoaryl triflate-type thienobenzyne precursors such as **1** could be prepared easily from 2,3-disubstituted 6-hydroxybenzo[*b*]thiophenes in two steps: iodination and triflylation. We also assumed that these simple 2,3-disubstituted benzothiophenes could be prepared easily from an anisole derivative by means of several established methods. Moreover, we were interested in investigating the regioselectivity in the reactions of thieno[4,5-*c*]benzynes **I** (6,7-thienobenzynes) with unsymmetric arynophiles or nucleophiles, and comparing the results with those reported for other ring-fused benzynes such as 3,4-cyclobutabenzyne,[11a] 6,7-indolyne,[11b] and thiazolobenzynes.[9e] Herein, we report an efficient method for the generation of thienobenzynes and their application to the synthesis of multisubstituted benzothiophenes.

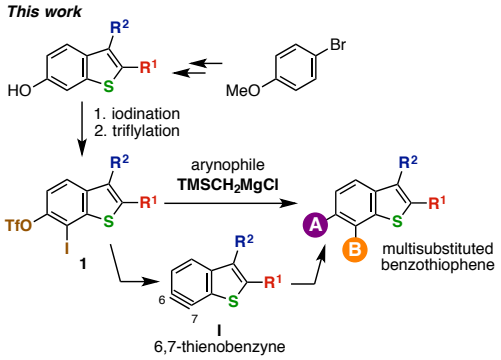
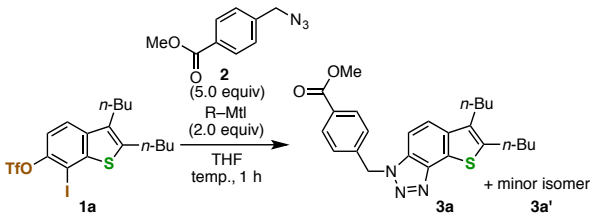


Figure 2. Thienobenzynes: new entries as ring-fused benzynes.

Toward a tetrasubstituted benzo[*b*]thiophene synthesis, we prepared 2,3-dibutyl-6-hydroxybenzo[*b*]thiophene from 4-bromoanisole, 5-decyne, and elemental sulfur in four steps based on the method reported by Wu and Yoshikai[5e] and derived it to *ortho*-iodoaryl triflate **1a** by regioselective iodination and subsequent triflylation.[12] Using a mixture of **1a** and methyl 4-(azidomethyl)benzoate (**2**, 5.0 equiv) in THF, we screened for the reaction conditions that allowed for the efficient generation of thienobenzyne (Table 1). Although treatment of the mixture with *n*-butyllithium[10a] or isopropylmagnesium chloride–lithium chloride complex[10b] at −78 °C afforded the desired cycloadduct **3a** only in low yields (entries 1 and 2), treatment with (trimethylsilyl)methylmagnesium chloride gave **3a** in high yield with high regioselectivity (entry 3). These results were in good agreement with our previous studies regarding the generation of thiazolobenzynes and 3-triflyoxyarynes,[9] indicating the advantage of the silylmethyl Grignard reagent with low nucleophilicity for generating arynes from *ortho*-iodoaryl triflates. The reaction using a small excess of azide **2** and the activator also proceeded smoothly to afford **3a** in sufficient yield (entry 4). The reaction performed at a higher temperature such as 0 °C significantly decreased the yield and regioselectivity (entry 5).

Table 1. Optimization of the reaction conditions



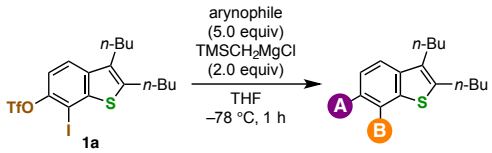
Entry	R–MtI	Temp. (°C)	Yield (%)[a]
1	*n*-BuLi	–78	25 (98:2)
2	*i*-PrMgCl·LiCl	–78	31 (98:2)
3	$TMSCH_2MgCl$	–78	93[b] (97:3)
4[c]	$TMSCH_2MgCl$	–78	80 (97:3)
5	$TMSCH_2MgCl$	0	58[b] (87:13)

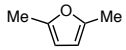
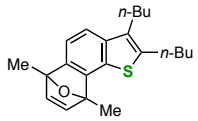
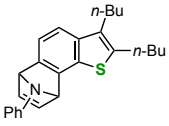
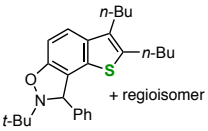
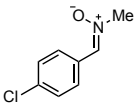
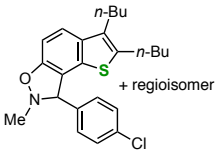
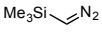
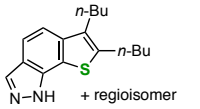
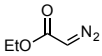
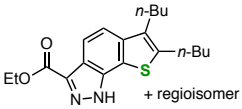
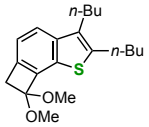
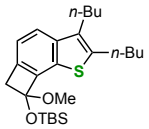
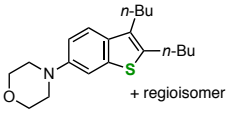
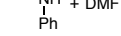
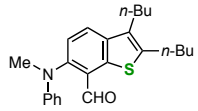
[a]Combined yields of **3a** and **3a'** based on ^{1}H NMR analyses, unless otherwise noted. The ratio of the regioisomers (**3a**:**3a'**) is shown in parentheses. [b]Combined yields of isolated **3a** and **3a'**. [c]Azide **2** (1.2 equiv) and $TMSCH_2MgCl$ (1.2 equiv) were used.

Under the best of conditions (Table 1, entry 3), a variety of multisubstituted benzothiophenes were successfully prepared via the thienobenzyne intermediate generated in situ from the precursor **1a** (Table 2). Diels–Alder reaction between the thienobenzyne and 2,5-dimethylfuran (**4**) or *N*-phenylpyrrole (**6**) afforded efficiently the cycloadducts **5** and **7**, respectively (entries 1 and 2). Cycloaddition with nitrone **8** or **10** also proceeded smoothly to yield oxazole-fused benzothiophenes **9** and **11**, respectively, in high yields with high regioselectivity (entries 3 and 4). Diazo compounds such as **12** and **14** participated in this reaction to afford imidazole-fused benzothiophenes **13** and **15**, respectively, albeit with low regioselectivity (entries 5 and 6). Cyclobutene-fused benzothiophenes **17** and **19** were obtained as a single isomer via [2+2] cycloaddition with ketene acetal **16** or **18**, respectively (entries 7 and 8). Nucleophilic addition of amines to the thienobenzyne also took place; the reaction with morpholine (**20**) afforded a mixture of 6- and 7-morpholinobenzothiophenes **21** and **21'** with moderate selectivity (entry 9). Furthermore, 6,7-difunctionalized benzothiophene **23** was obtained via addition of *N*-methylaniline (**22**) to the thienobenzyne followed by formylation with *N*,*N*-dimethylformamide (DMF).[13]

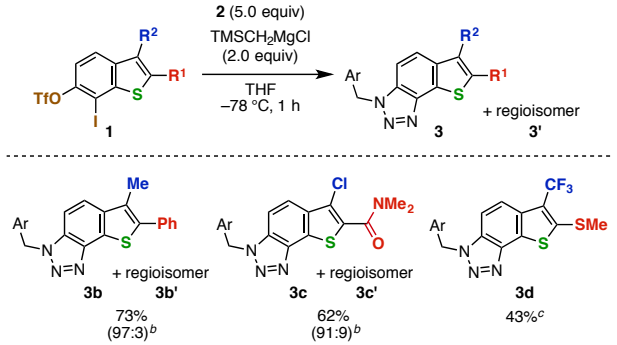
The method was also applicable for the generation of 6,7-thienobenzynes bearing various substituents at their C2- and C3-positions, significantly expanding the scope of available benzothiophenes such as **3b**–**d** (Scheme 1). The corresponding precursors **1** could be easily derived from simple benzothiophenes, which were prepared in short steps by several methods depending on the C2- and C3-substituents.[12] Cycloaddition of 3-methyl-2-phenyl-6,7-thienobenzyne with azide **2** afforded 1,2,3-triazole-fused benzothiophene **3b** with a small amount of regioisomer **3b'** in a high combined yield. Benzothiophene **3c** bearing an amide, an ester, and chloro moieties was also obtained from the corresponding thienobenzyne precursor leaving these functional groups untouched. Furthermore, 2-methylthio-3-trifluoromethyl-6,7- thienobenzyne also participated in this reaction to furnish benzothiophene **3d**.

Table 2. Cycloadditions of 6,7-thienobenzyne



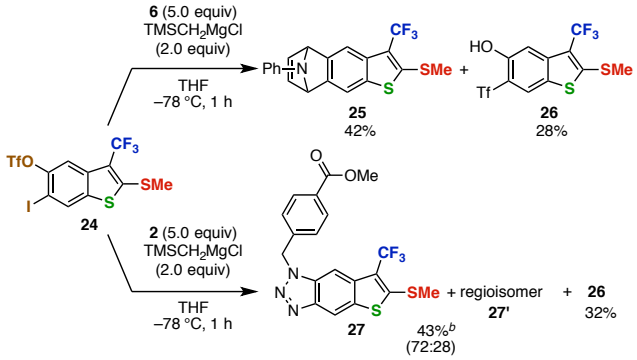
Entry	Arynophile		Product		yYield (%)[a]
1		**4**		**5**	81
2		**6**		**7**	92
3		**8**		**9** + **9'**	93 (84:16)
4		**10**		**11** + **11'**	79 (81:19)
5		**12**		**13** + **13'**	91 (52:48)
6		**14**		**15** + **15'**	71 (77:23)
7		**16**		**17**	80[b]
8		**18**		**19**	86[b]
9		**20**		**21** + **21'**	91 (70:30)
10		**22**		**23**	34[b]

[a]Isolated yields. When regioisomers were obtained, the combined yields are shown. The ratio of the regioisomers based on ^{1}H NMR analysis by using 1,1,2,2-tetrachloroethane as an internal standard is shown in parentheses. [b]Regioisomer was not detected.



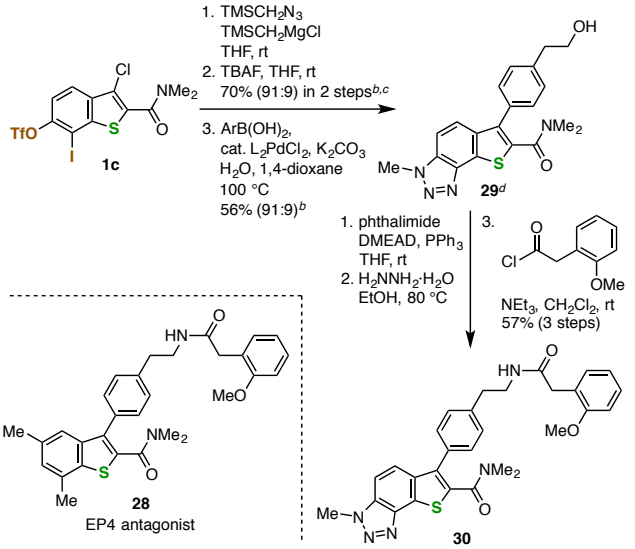
Scheme 1. Cycloadditions of various 2,3-disubstituted 6,7-thienobenzynes[a]. [a]Ar = *p*-(MeO$_2$C)C$_6$H$_4$-. Isolated yields are shown. When regioisomers were obtained, the combined yields are shown. [b]The ratio of the regioisomers. [c]Regioisomer was not detected.

A 5,6-thienobenzyne was similarly generated as demonstrated using precursor **24** (Scheme 2). The reaction with pyrrole **6** afforded the cycloadduct **25** in moderate yield. The reaction with azide **2** afforded a regioisomeric mixture of cycloadducts **27** and **27'** in moderate yield with moderate selectivity. In these cases, a considerable amount of triflone **26**, formed via the thia-Fries rearrangement,[9b,f,14] was also obtained. This side reaction must have facilitated by the strong electron-withdrawing effect of the trifluoromethyl group, which contributed to stabilize the anionic intermediate, generated via the iodine–magnesium exchange reaction.



Scheme 2. Cycloadditions of 5,6-thienobenzyne.[a] [a]Isolated yields are shown. [b]Combined yield of isolated regioisomers. The ratio of the regioisomers is shown in parentheses.

By using a thienobenzyne intermediate, we prepared a ring-fused analog of the potent prostaglandin E$_2$ subtype 4 receptor (EP4) antagonist **28** (Scheme 3).[15] To demonstrate the utility of our approach in diversifying the substituents on the benzo-moiety of **28**, we aimed to alter the core 5,7-dimethylbenzothiophene structure to a triazole-fused benzothiophene structure such as that of **30**. Thus, cycloaddition of a thienobenzyne generated from the precursor **1c** with trimethylsilylmethyl azide, followed by desilylprotonation and Suzuki–Miyaura cross-coupling with an arylboronic acid afforded **29** containing a small amount of regioisomer. After removal of the regioisomer by recrystallization, the hydroxy group of **29** was converted to an amino group by the Mitsunobu method. Finally, acylation afforded the desired EP4 antagonist analog **30**.



Scheme 3. Synthesis of an EP4 antagonist analog.[a] [a]Isolated yields are shown. Ar = *p*-(HOCH$_2$CH$_2$)C$_6$H$_4$; L = *p*-(Me$_2$N)C$_6$H$_4$P(*t*-Bu)$_2$; DMEAD = di(2-methoxyethyl) azodicarboxylate. [b]The ratio of the regioisomers is shown in parentheses. [c]A mixture of regioisomers was used. [d]**29** was obtained by recrystallization.

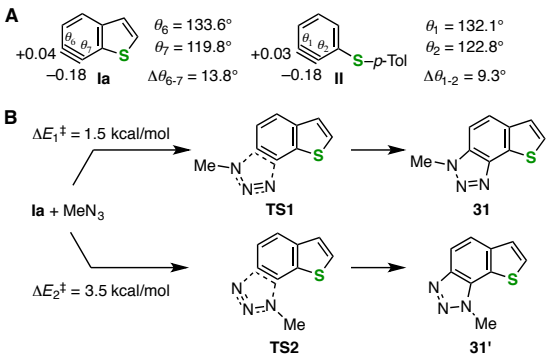


Figure 3. Computational studies using a DFT method (M11-L/6-31G(d)). (A) Optimized structures of 6,7-thienobenzyne (**Ia**) and 3-(4-tolylthio)benzyne (**II**). The numbers show the charge distribution. (B) Analysis of the reaction pathway for cycloadditions of **Ia** with methyl azide.

Theoretical studies based on density functional theory (DFT) provided insights into the regioselectivity observed in the reactions of thienobenzynes (Figure 3). We optimized the structure of 6,7-thienobenzyne (**Ia**) at the M11-L/6-31G(d) level of theory using the GAMESS-US program package.[16] As in our previous study on thiazolobenzynes,[9e] the optimized geometry structure of **Ia** agreed well with that previously reported by Paton, Houk, Garg, and coworkers.[17] The internal angle at C6 in optimized **Ia** was larger than that of C7, showing the highly distorted structure of thienobenzyne (Figure 3A). Population analysis also indicated higher electrophilicity at C6 than C7.[18] The magnitude of the distortion in **Ia** was greater than that of optimized 3-(4-tolylthio)benzyne (**II**), indicating that increase of strain, induced by the fused ring, enhanced the distortion of thienobenzyne as in the other ring-fused arynes.[7o,9e,11,17] The difference between the internal angles of distorted aryne triple bond ($\Delta\theta$) in **Ia** was larger than that in **II**, which was in good agreement with the higher regioselectivity observed for the reaction of thienobenzyne generated from **1a** with azide **2** (distal:proximal = 97:3 at −78 °C; Table 1, entry 3)

than our previously reported reaction of 3-(4-tolylthio)benzyne with benzyl azide (distal:proximal = 83:17 at −78 °C).[8c] In both **Ia** and **II**, as in the case of thiazolobenzyne,[9e] the increased *p* character of the C–S bond,[19] which renders the distal carbon of aryne triple bond more electron deficient,[11a] should be also entertained as a significant factor that distorts the aryne structure. Further theoretical analysis at the same level of theory provided transition state (TS) structures for the cycloadditions between **Ia** and methyl azide (Figure 3B). The calculated activation energy for the distal cycloaddition via **TS1** was 2.0 kcal/mol smaller than that for the proximal cycloaddition via **TS2**, which was in good agreement with the observed regioselectivity (Table 1, entry 3).

In summary, we have added thienobenzynes as a new entry into an aryne toolbox, demonstrating that they serve as useful intermediates for diverse multisubstituted benzothiophenes. Further studies to expand the scope of the method and application to the synthesis of bioactive compounds are now in progress.

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Supporting Information for characterization of new compounds is available electronically on J-STAGE.

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