Expanding the synthesizable multисubstituted benzo[b]thiophenes via 6,7-thienobenzenes generated from o-silylaryl triflate-type precursors†

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Various 2,3-disubstituted 6,7-thienobenzenes have been efficiently generated from the corresponding o-silylaryl triflate-type precursors by activation with fluoride ions. The method has expanded the scope of synthesizable multисubstituted benzo[b]thiophenes, including those with various heteroatom substituents, and can be applied to the synthesis of EP4 antagonist analogs.

Introduction

Benzo[b]thiophene is one of the structural units frequently found in molecules applied in various research fields, including medicinal chemistry and materials science.1–3 Although multисubstituted benzo[b]thiophenes are promising compounds as pharmaceutical and organic material candidates, their synthetic approaches are limited.4 To improve this situation, we previously reported a facile method to prepare various tetrasubstituted benzo[b]thiophenes via thienobenzyne intermediates such as I (Fig. 1A).3 Thienobenzenes I were efficiently generated from o-iodoaryl triflate-type precursors by treatment with a silylmethyl Grignard reagent at −78 °C, rendering a diverse range of tetrasubstituted benzo[b]thiophenes easily available.5 We considered that the use of o-silylaryl triflate-type thienobenzyne precursors would further expand the scope of the synthesizable benzo[b]thiophenes (Fig. 1B). This is because generation of arynes from this type of precursor has been generally achieved under mild conditions using a basic activator such as the fluoride ion.6–8 Indeed, a wide range of aromatic compounds have become easily available via the transformation of arynes generated from o-silylaryl triflate-type precursors. Herein, we report the synthesis of o-silylaryl triflate-type 6,7-thienobenzenes, the generation of aryne species from these precursors, and the application of the method to the synthesis of various benzo[b]thiophenes including potent analogs of a prostaglandin E receptor subtype 4 (EP4) antagonist.

Results and discussion

Synthesis of thienobenzyne precursors

Similar to our previous synthesis of o-iodoaryl triflate-type 6,7-thienobenzenes, o-silylaryl triflate-type precursors 2a–d were successfully prepared from the corresponding 2,3-disubstituted 6-hydroxybenzo[b]thiophenes 1a–d (Schemes 1 and 2).5 Benzo[b]thiophenes 2a–c were prepared from 6-hydroxybenzo[b]thiophenes 1a–c according to the facile synthetic method for o-silylaryl triflates from phenols as reported by Garg and coworkers; carbamate formation using isopropyl isocyanate, regioselective C-silylation via ortho-lithiation, removal of the directing group, and triflylation (Scheme 1).9 Although preparation of benzo[b]thiophene 2d, bearing a chloro and an amide group, from phenol 1d by the same method was unsuccessful at the step of C-silylation via ortho-lithiation, the C-

† Electronic supplementary information (ESI) available: Experimental procedures, characterization for new compounds including NMR spectra. See DOI: 10.1039/c8ra04035d
silylated product was obtained by an alternative method (Scheme 2). Thus, regioselective iodination of phenol 1d with a morpholine–iodine complex, followed by O-silylation and treatment with the turbo Grignard reagent to promote the iodine–magnesium exchange reaction and subsequent retro-Brook rearrangement via the anionic intermediate II, afforded o-silylphenol 4, leaving the chloro and amide groups untouched. Finally, triﬂylation of 4 afforded the desired 2d. Performing the retro-Brook rearrangement and subsequent O-triﬂylation in one-pot procedure afforded 2d in 13% yield.

Optimization of the reaction conditions for generation of thienobenzenes

The efficient conditions for generating 6,7-thienobenzene were screened for the reaction between precursor 2a and azide 5a in tetrahydrofuran (THF) at room temperature, which revealed that various ﬂuoride sources or cesium carbonate with 18-crown-6 were effective as an activator (Table 1). For example, the activation of 2a with potassium ﬂuoride in the presence of 18-crown-6 afforded the desired cycloadduct 6a with a small amount of regioisomer 6a′ (entry 1). The regioselectivity was slightly lower than that observed in the reaction using o-iodoaryl triﬂate-type 6,7-thienobenzene precursor probably because the reaction triggered by silicate formation was conducted at a higher temperature. Tetra(n-butyl)ammonium difluoro(triphenyl)silicate and tetra(n-butyl)ammonium ﬂuoride also served as good activators without any additives (entries 2 and 3). While using potassium ﬂuoride alone was ineffective (entry 4), 2a was effectively activated with cesium ﬂuoride, resulting in the highest combined yield of cycloadducts 6a and 6a′ (entry 5). Considering that the generation of benzene from o-(trimethylsilyl)phenyl triﬂate with cesium ﬂuoride in THF was reported as inefﬁcient, this result suggests that thienobenzene precursor 2a is more easily activatable than the simple o-silylphenyl triﬂate. Decreasing the amount of azide 5a to 2.0 equiv. slightly lowered the yield of 6a/6a′ (entry 6). In addition, 6,7-thienobenzene was also generated efﬁciently under ﬂuoride-free conditions using cesium carbonate and 18-crown-6 (entry 7).

### Table 1 Optimization of the reaction conditions

| Entry | Activator | Additive | Yielda (%) |
|-------|-----------|----------|------------|
| 1     | KF        | 18-Crown-6 | 78 (89 : 11) |
| 2     | n-Bu4NF   | —        | 73 (90 : 10) |
| 3     | n-Bu4NF   | —        | 69 (91 : 9)  |
| 4     | KF        | —        | 0           |
| 5     | CsF       | —        | 84 (90 : 10) |
| 6     | CsF       | —        | 74 (89 : 11) |
| 7     | Cs4CO3    | 18-Crown-6 | 75 (89 : 11) |

a Isolated yield. b Reaction was performed at 0 °C. c Azide 5a (2.0 equiv.) was used.

Synthesis of various multisubstituted benzothiophenes via thienobenzenes

Under the optimal conditions, various arynophiles reacted efﬁciently with thienobenzene generated from 2a to afford multisubstituted benzothiophenes in high yields (Fig. 2). These include cycloadducts 7, 8, 9, and 10 obtained from the reactions with 2,5-dimethylfuran, N-phenylpyrrole, N-(tert-butyl)-α-phenyl nitron, and 1,1-dimethoxyethylene, respectively. The nucleophilic addition of morpholine to the 6,7-thienobenzene also took place, affording 6-morpholinobenzothiophene 11 as the major product. The regioselectivity observed using unsymmetrical arynophiles and the nucleophile showed similar trends to their reactions with the same thienobenzene species generated from the o-iodoaryl triﬂate-type precursor.

An abundance of utilizable transformations is a great advantage of using o-silylaryl triﬂates as aryne precursors over the other types. Indeed, the utility of o-silylaryl triﬂate-type 6,7-thienobenzene precursor was demonstrated through several unique transformations that we recently developed (Fig. 3). For example, the Michaelis–Arbuzov-type reaction of the
thienobenzene generated from 2a with alkoxysilane 12 proceeded smoothly, affording a high yield of aryloxysilane diamide 13 as the sole product (Fig. 3A).14a Furthermore, difunctionalization of the thienobenzene intermediate with alkoxysilane 12, sulfoximine 16, and sulfoxide 18 resulted in the selective formation of thioaminated or oxythiolated benzothiophenes 15/15’, 17, and 19, respectively, which are difficult to prepare by conventional methods (Fig. 3B). The yields of thioaminated products 15/15’ and 17 were improved under modified conditions wherein the reactions were carried out at a higher temperature in 1,4-dioxane.

Various 2,3-disubstituted 6,7-thienobenzens were also generated from precursors 2b–d (Fig. 4). The reactions of these thienobenzens with azide 5a afforded triazole-fused 3-methyl-2-phenyl-2-methylsulfanyl-3- trifluoromethyl, and 3-chloro-2-(dimethy lamino)carbonylbenzothiophene derivatives 6b/6b’, 6c, and 6d/6d’, respectively, in a regioselective manner. Cycloadduct 6d was obtained as a single isomer along with complex mixtures of side-products probably due to the effect of the electron-withdrawing trifluoromethyl group. A similar trend was observed in our previous study,3 wherein 6c was obtained without formation of the regioisomer using o-iodoaryl triflate-type aryne precursor activated with a silylmethyl Grignard reagent.

**Synthesis of the analogs of an EP4 antagonist**

The utility of this method was demonstrated in the facile diversification of the benzo-moiety of the EP4 antagonist 20a developed by Li and coworkers (Scheme 3).15 The analogs 20b–d with methytri azole-fused, benzo-fused, or morpholino-substituted benzo thiophene structure, respectively, were easily prepared via the reactions of the thienobenzene intermediate generated from 2d with (trimethylsilyl)methyl azide, furan, and morpholine, affording adducts 21a–c as the major products. According to the modified method reported previously for the derivatization of 21a to 20b,5 EP4 antagonist analogs 20c and 20d were prepared by the Suzuki–Miyaura cross-coupling, the Mitsunobu-type C–N bond formation followed by treatment with hydrazine, and amidation. Evaluations of the EP4 receptor binding affinities showed that benzo-fused analog 20c (Ki = 0.18 μM) is a potent EP4 antagonist comparable to the original compound 20a (Ki = 0.25 μM), while methyltri azole-fused analog 20b (Ki = 0.47 μM) and morpholino-substituted analog 20d (Ki = 0.70 μM) are slightly weaker antagonists than 20a.16 This result suggests a possibility for developing more potent EP4 antagonists by further modification of the benzo-moiety of 20a.

**Fig. 2** Reactions of thienobenzene generated from 2a with various arynes. (a) Reaction with 2,5-dimethylfuran. (b) Reaction with N-phenylpyrrole. (c) Reaction with N-(tert-butyl)-α-phenyl nitronate. (d) Reaction with 1,1-dimethoxyethylene. (e) Reaction with morpholine.

**Fig. 3** Transformations via thienobenzene generated from 2a, involving C–P, C–S, C–N, and C–O bond formations. (A) Reaction with alkoxysilane 12. (B) Reactions with sulfinimine 14, sulfoximine 16, and sulfoxide 18. See the ESI† for details.
Conclusions

This study showed that 7-silyl-6-triflyloxybenzo[θ]thiophenes served as useful precursors of 6,7-thienobenzynes, thus expanding the range of synthesizable multisubstituted benzo-thiophenes. The utility of the method was demonstrated for the synthesis of various heteroatom-substituted benzo-thiophenes and the facile structural diversification of an EP4 antagonist that resulted in identification of a potent analog.

Conflicts of interest

There are no conflicts to declare.

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