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Sequential Molecular Conjugation using Thiophene *S*,*S*-Dioxides Bearing a Clickable Functional Group

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Sequential Molecular Conjugation using Thiophene *S*,*S*-Dioxides Bearing a Clickable Functional Group

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Electron-deficient thiophene dioxides have been found to react rapidly with a bicyclo[6.1.0]non-4-yne derivative to afford benzocyclooctenes in excellent yields. Thiophene dioxides bearing a clickable functional group served as efficient bisreactive platform molecules that enabled sequential molecular conjugation in a simple operation.

Keywords: Thiophene *S*,*S*-dioxide | Cyclooctyne | Diels–Alder reaction

Inverse electron demand Diels–Alder (IEDDA) reactions between electron-deficient dienes and electron-rich dienophiles have been used widely to conjugate molecules covalently across a broad range of research fields such as materials, pharmaceuticals, and life sciences.[1] In particular, reactions of 1,2,4,5-tetrazines with *t*-cyclooctenes or cyclooctynes have been applied extensively to bioconjugation as these reactions proceed rapidly in a bioorthogonal manner (Figure 1A).[2] However, despite rapid advances in click chemistry in recent years,[3,4] including the IEDDA reactions,[5] the synthesis of multifunctional molecules via sequential conjugation of functional modules to a platform molecule bearing several connectable groups is not easy.[6,7] This is due to the lack of user-friendly conjugation reactions that are orthogonal to each other.

During the course of our studies on strained alkyne chemistry,[8] we found that cyclooctyne derivatives bearing a terminal alkyne moiety serve as efficient bisreactive platforms for conjugation of two ynophiles such as azides; treatment of the platform diyne with an excess amount of a copper salt enabled selective click reaction at the terminal alkyne moiety via the transient protection of the higher azidophilic strained alkyne moiety by complexation with copper.[8c] We assumed that finding a novel combination of a reaction that is capable of connecting two molecules efficiently would be of benefit in achieving the convergent synthesis of multifunctional molecules via sequential conjugation. Herein, we report that a thiophene *S*,*S*-dioxide[9] reacts smoothly with a cyclooctyne and that thiophene *S*,*S*-dioxides bearing a clickable functional group serve as efficient bisreactive platforms for sequential conjugation.

From a literature search, we found a pioneering study on the Diels–Alder reaction between 3,4-di(*tert*-butyl)thiophene *S*,*S*-dioxide (**4**) and cyclooctyne (**5**) reported by Nakayama and coworkers in 1988; the reaction was performed in refluxing *o*-dichlorobenzene (180 °C) to afford benzocyclooctene **6**, which was formed with the release of sulfur dioxide through cheletropic reaction of the initial cycloadduct (Figure 1B).[9d] We assumed that using a thiophene dioxide bearing electron-withdrawing groups in combination with a more strained dienophile would render the reaction feasible under milder conditions that would suit our purpose. Based on this idea, we screened for the highly reactive dienophile in the reaction with commercially available 3,4-dichlorothiophene *S*,*S*-dioxide (**7a**) in methanol and found that bicyclo[6.1.0]non-4-yne (BCN) derivative **2**[4c] reacted smoothly with **7a** even at room temperature to afford the desired benzocyclooctene **8a** in high yield (Figure 1C).

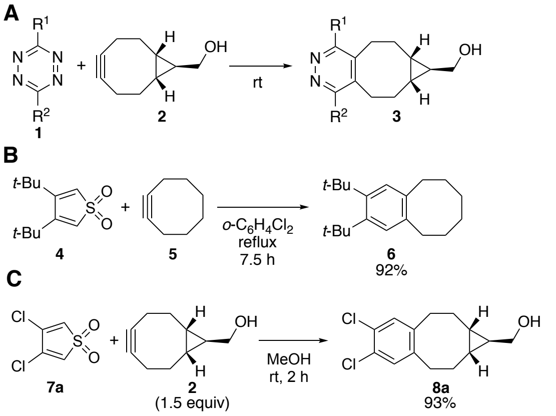
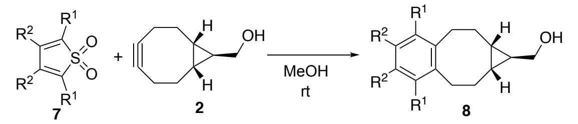


Figure 1. (A) Reported reaction of tetrazines **1** with BCN derivative **2**. (B) Reported reaction between thiophene dioxide **4** and cyclooctyne (**5**). (C) Reaction of thiophene dioxide **7a** with BCN derivative **2**.

Table 1. Reactions of various thiophene *S*,*S*-dioxides with **2**

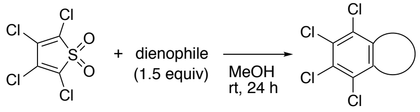


Entry	R^1	R^2	**7**	LUMO (eV)[a]	**8**	Yield/%[b]	k ($M^{-1}s^{-1}$)[a,c]	k_{rel}
1	H	Cl	**7a**	–2.91	**8a**	96	9.9×10^{-2}	1
2	H	Br	**7b**	–2.93	**8b**	quant.	0.26	2.6
3	Br	H	**7c**	–2.79	**8c**	quant.	9.1×10^{-2}	0.82
4	I	H	**7d**	–2.73	**8d**	quant.	7.7×10^{-3}	0.077
5	Cl	Cl	**7e**	–3.09	**8e**	93	1.7	17
6	Br	Br	**7f**	–3.09	**8f**	quant.	0.98	9.9
7	$SiMe_3$	H	**7g**	–2.15	**8g**	no reaction	–	–
8	C_6H_4-*p*-OMe	H	**7h**	–2.18	**8h**	no reaction	–	–
9	C_6H_4-*p*-CF_3	H	**7i**	–3.09	**8i**	53	–	–

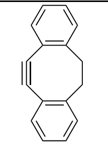
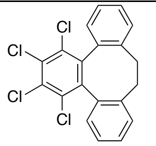
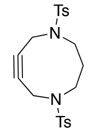
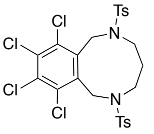
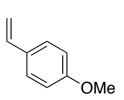
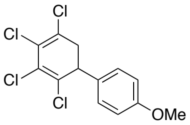
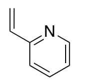
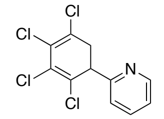
[a] See Supporting Information for details. [b] Isolated yields of the reactions of **7** (1.0 equiv) with **2** (1.5 equiv) in methanol at room temperature. [c] The second-order rate constants of the reactions at 25 °C.

Electronic and steric effects of substituents on thiophene dioxides greatly affected the reactivity with BCN derivative **2** (Table 1). For example, in addition to **7a** (entry 1), various halogenated thiophene dioxides **7b**–**7f** also reacted smoothly with **2** to afford the corresponding benzocyclooctenes **8b**–**8f** in excellent yields (entries 2–6). In particular, time-dependent absorption analyses, which we conducted to determine the second-order rate constants (*k*) of the reactions, indicated significantly high reactivity of tetrachloro- and tetrabromo-substituted thiophene dioxides, **7e** and **7f**, which reacted more than tenfold faster than 3,4-dichlorothiophene dioxide **7a** (entries 5 and 6). While 3,4-dibromothiophene dioxide **7b** showed slightly higher reactivity than **7a** (entry 2), almost the same or decrease in reaction rates were observed for 2,5-dibromo- and 2,5-diiodothiophene dioxide, **7c** and **7d**, respectively (entries 3 and 4). The reactivities of thiophene dioxides **7a**–**7f** showed good correlations with their LUMO energies obtained by DFT calculations (B3LYP/6-31G(d)); the reaction rate increased as the energy of LUMO decreased, indicating that electron-withdrawing groups on the thiophene dioxide contributed to the acceleration of the reaction as with the general IEDDA reaction. In stark contrast, 2,5-bis(trimethylsilyl)- and 2,5-di(4-methoxyphenyl)-substituted thiophene dioxide, **7g** and **7h**, with high LUMO levels did not react with BCN derivative **2** at room temperature (entries 7 and 8). Even 2,5-di(4-trifluoromethylphenyl)thiophene dioxide **7i** with a LUMO level as low as **7e** and **7f** reacted with **2** slowly and afforded the corresponding benzocyclooctene **8i** only in moderate yield (entry 9). These results clearly show that substituents at 2,5-positions considerably decreased the reactivity of thiophene dioxides due to steric hindrance.

Table 2. Reactions of tetrachlorothiophene *S*,*S*-dioxide (**7e**) with various dienophiles

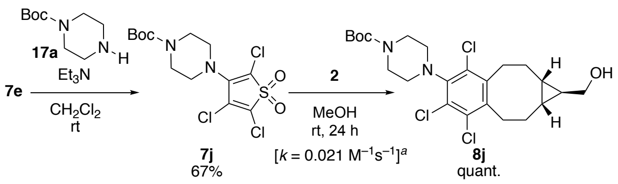


7e

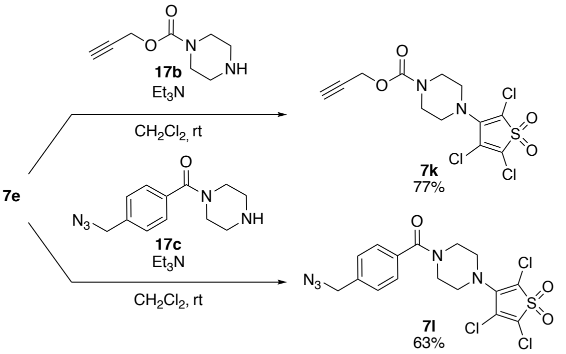
Entry	Dienophile		Product		Yield/%[a]	k ($M^{-1}s^{-1}$)[b]
1		**9**		**10**	6[c] (84)[d]	–
2		**11**		**12**	15[c] (63)[e]	–
3		**13**		**14**	91	5.5 × 10^{-3}
4		**15**		**16**	72	7.8 × 10^{-4}

[a] Isolated yields, unless otherwise noted. [b] See Supporting Information for details. [c] Yields based on ^{1}H NMR analysis by using 1,1,2,2-tetrachloroethane as an internal standard. [d] Yield when the reaction was performed at 50 °C for 72 h is shown in parentheses. [e] Yield when the reaction was performed at 50 °C for 24 h is shown in parentheses.

Dienophiles other than BCN derivative **2** also reacted with tetrachlorothiophene dioxide **7e**, although the reaction rate differed depending on the substrate (Table 2). Dibenzo-fused cyclooctyne **9**[4b] and 4,8-diazacyclononyne **11**,[4d] which react rapidly with azides like BCN derivative **2**, showed significantly lower reactivity with **7e** than **2** at room temperature (entries 1 and 2). These reactions slowly proceeded with heating at 50 °C to afford the corresponding products in good yields. Similar to the previous reports,[9c] 4-methoxystyrene (**13**) and 2-vinylpyridine (**15**) also reacted with **7e** to afford dihydrobenzenes **14** and **16**, respectively, although the reactions were not as fast as that with **2** (entries 3 and 4). The rates of these reactions were comparable to those between azides and cyclooctynes, which have been frequently used as reliable click reactions.



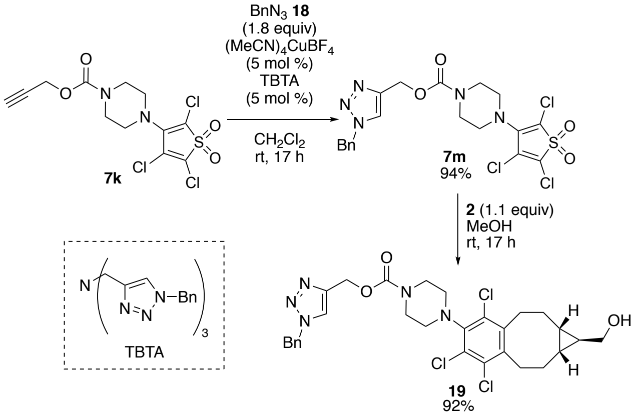
Scheme 1. Synthesis of *N*-Boc-piperazino-substituted trichlorothiophene dioxide **7j** and its reaction with BCN derivative **2**. [a] See Supporting Information for details.



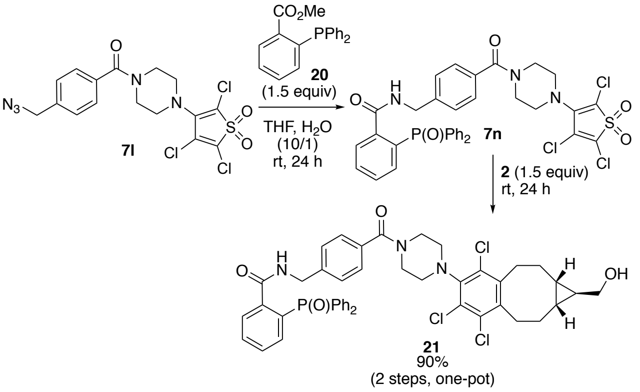
Scheme 2. Synthesis of piperazino-substituted trichlorothiophene dioxides **7k** and **7l** bearing a terminal alkyne or azido moiety.

We then embarked on a study to develop a thiophene dioxide bearing a connectable group such as a clickable terminal alkyne or azido moiety. To elaborate such a bisreactive molecule, we focused on tetrachlorothiophene dioxide **7e**. Considering the nuclephilic displacement observed in the related compound, we assumed that **7e** would show electrophilic reactivity similar to that of halogenated electron-deficient olefins.[10] Indeed, treatment of tetrachlorothiophene dioxide **7e** with *N*-Boc-piperazine (**17a**) in the presence of triethylamine at room temperature selectively afforded *N*-Boc-piperazino-substituted trichlorothiophene dioxide **7j** with a small amount of the isomer (1%) (Scheme 1).[11] The reaction of **7j** with BCN derivative **2** smoothly proceeded at a sufficient rate to afford the corresponding product **8j** quantitatively. This result suggested that one chloro group of **7e** is replaceable by the other group without significantly affecting the ynophilicity. Based on these results, we prepared two bisreactive thiophene dioxides **7k** and **7l** bearing a clickable terminal alkyne or azido group via the reaction with **7e** and the corresponding piperazine derivative **17b** or **17c**, respectively (Scheme 2).

Bisreactive thiophene dioxides **7k** and **7l** were successfully applied to sequential conjugation (Schemes 3 and 4). For example, copper-catalyzed azide–alkyne cycloaddition of **7k** with benzyl azide (**18**) resulted in the formation of triazole **7m**, leaving the chloro groups and the thiophene dioxide moiety untouched (Scheme 3). Subsequent reaction between thiophene dioxide **7m** and BCN derivative **2** furnished the cycloadduct **19** in high yield. Furthermore, a simple one-pot operation involving the Staudinger–Bertozzi ligation of azide-functionalized thiophene dioxide **7l** with phosphine **20**, followed by cycloaddition between the resulting amide **7n** and **2** afforded the conjugate **21** in high yield (Scheme 4). These results clearly indicate that thiophene dioxides **7k** and **7l** would serve as efficient platforms for preparing a variety of compounds, including multifunctional molecules, from simple modules.



Scheme 3. Sequential conjugation using **7k** via copper-catalyzed Huisgen reaction with **18** followed by the Diels–Alder reaction with **2**.



Scheme 4. Sequential conjugation using **7l** via the Staudinger–Bertozzi ligation with **20** followed by the Diels–Alder reaction with **2**.

In summary, we have demonstrated that thiophene dioxides bearing multiple small halogeno groups react rapidly with a bicyclononyne derivative.[12,13] We have also shown that electron-deficient thiophene dioxides bearing a connectable group, which were easily prepared from tetrachlorothiophene dioxide, served as good bisreactive platform molecules, enabling efficient sequential conjugation in a simple manner. Further applications for the facile synthesis of multifunctional molecules based on the use of thiophene dioxides are currently under way in our laboratory.

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Supporting Information is available on http://dx.doi.org/10.1246/cl.xxxxxx.

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11 See Supporting Information for details.

12 A part of this work was presented in 2014, see: T. Meguro, Y. Yoshida, T. Hosoya, 25th Symposium on Physical Organic Chemistry, Sendai, Japan, Sep. 7, **2014**, Abstr., No. 1P004.

13 During prepartion of this manuscript, a rapid generation of sulfur dioxide via the reaction of tetrachlorothiphene dioxide with a BCN derivative was reported. See: W. Wang, X. Ji, Z. Du, B. Wang, *Chem. Commun.* **2017**, *53*, 1370.