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Editor's Choice

Synthesis of Diverse Benzotriazoles from Aryne Precursors Bearing an Azido Group via Inter- and Intramolecular Cycloadditions

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A diverse range of benzotriazoles were synthesized from various 3-(azidoalkoxy)aryne precursors, which were easily prepared by Mitsunobu etherification. Various bis-1,2,3-triazoles containing a benzotriazole skeleton were obtained via sequential azide–alkyne and azide–aryne cycloadditions. Intramolecular azido–aryne cycloaddition, conducted using the same starting materials, afforded new types of ring-fused benzotriazoles. In the latter case, the reaction proceeded efficiently even though the regioorientation of the azido group was the reverse of that usually observed in intermolecular reactions between 3-alkoxyarynes and an azide.

Keywords: Aryne | Azide | Benzotriazole

Benzotriazole is a heterocyclic compound that often forms part of the core skeleton of bioactive compounds, including clinical drugs and drug candidates.[1] To address the increasing demand for chemical libraries that facilitate efficient drug discovery, we have constructed a chemical library comprising benzotriazoles bearing various pharmacophores.[2] Since benzotriazoles are easily prepared by cycloaddition reactions between arynes and azides,[3] arynes bearing a latently transformable group serve as useful intermediates for preparing a diverse range of benzotriazoles.[2,4,5] In this context, we recently reported a modular synthetic method for the preparation of diverse bis- and tris-1,2,3-triazoles, including the benzotriazole skeleton.[2b] This approach was based on the use of aryne precursors **pro-A** bearing a clickable terminal alkyne moiety (Figure 1A). Various bis-1,2,3-triazoles **B** were prepared from **pro-A** via sequential azide–aryne and azide–alkyne cycloadditions. Herein, we show that the azido-functionalized 3-alkoxyaryne precursors **pro-C** also serve as useful common platform molecules for the synthesis of diverse benzotriazoles such as bistriazoles **D** and new types of ring-fused benzotriazoles **E**, which were obtained via sequential intermolecular cycloadditions and an intramolecular cycloaddition, respectively (Figure 1B).

Various 3-(azidoalkoxy)aryne precursors, the starting materials used in this study, were easily prepared in a convergent manner using the Mitsunobu reaction[6] (Scheme 1). Commercially available resorcinols **1** were easily converted to 2-iodo-3-triflyloxyphenols **2** according to Suzuki's three-step protocol.[7,8] Dehydrative etherification of **2** with separately prepared azido-substituted alcohols **3** proceeded efficiently upon treatment with triphenylphosphine and diethyl azodicarboxylate to afford the corresponding aryne precursors **4a**–**4g** without damaging the azido group stemmed from iminophosphorane formation.[8]

The modular synthesis of benzotriazole-containing bis-1,2,3-triazoles was accomplished via sequential cycloadditions to the aryne precursors **4**: a copper(I)-catalyzed azide–alkyne cycloaddition (CuAAC),[9] followed by silylmethyl Grignard-triggered[2b,2c,5v] regioselective azide–aryne cycloaddition (Figure 2). This method enabled the facile synthesis of bistriazoles such as **8a**–**8c** bearing various functional groups, including silyl, ester, bromo, and pyridyl moieties, in moderate to high yield without isolation of the monotriazole intermediates.

During our attempt to perform the sequential cycloadditions in reverse order, we observed that a new type of ring-fused benzotriazole was also produced (Figure 3). From the reaction of an aryne generated from **4a** in the presence of excessive benzyl azide (**7a**), a small amount of tetracyclic compound **10a** was obtained in addition to the intermolecular cycloadduct **9a** (Figure 3A). This compound must be formed via an intramolecular

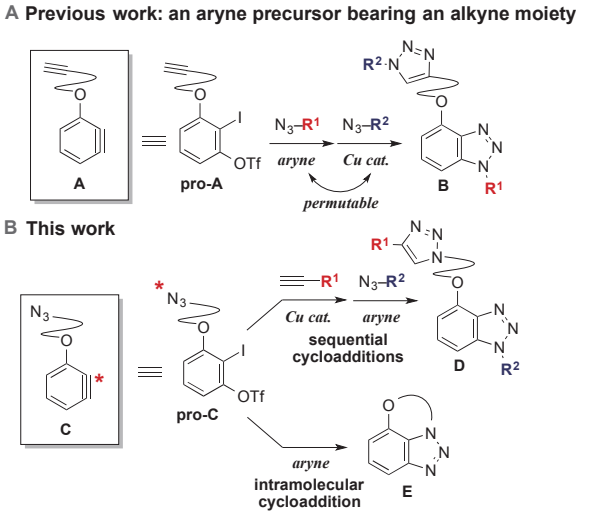
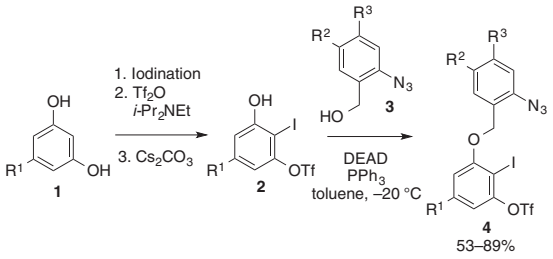


Figure 1. Versatile synthetic methods for the preparation of benzotriazoles. (A) Our previous work based on sequential cycloadditions of an aryne bearing an alkyne moiety. (B) This work based on the use of aryne precursors bearing an azido group. Tf = CF_3SO_2.



Scheme 1. Preparation of 3-(azidoalkoxy)aryne precursors.

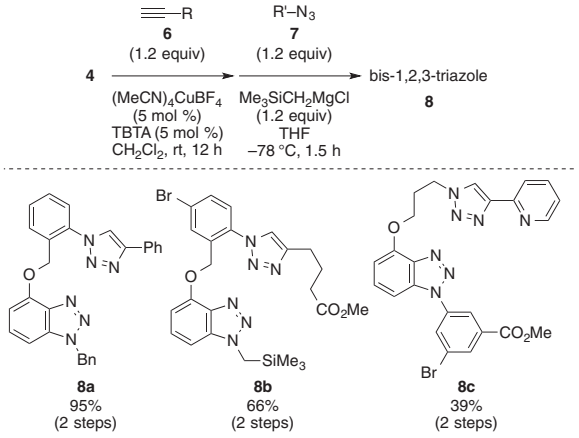


Figure 2. Synthesis of bistriazoles from **4** via sequential intermolecular azide–alkyne and azide–aryne cycloadditions.

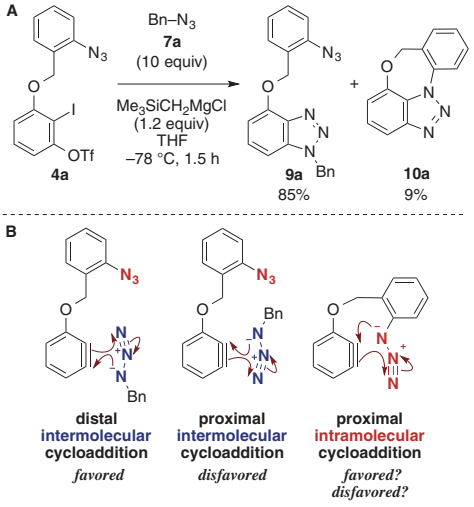
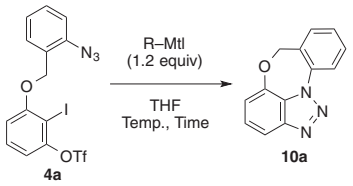


Figure 3. Inter- versus intramolecular azide–aryne cycloaddition.

azide–aryne cycloaddition. Similar to the formation of **9a**, intermolecular [3+2] cycloaddition between 3-alkoxybenzyne and an azide generally proceeds in a regioselective manner, owing to the inductive electron-withdrawing effect of the alkoxy group. This affords a cycloadduct, wherein the alkoxy group and the substituent on the azide are placed distal to each other (Figure 3B).[2b–2d,3a,3b] Because we were interested in the formation of new types of compact ring-fused heterocycles obtained through the proximal mode of cycloaddition, which is usually disfavored, we further examined this unusual intramolecular reaction.

We optimized the reaction conditions for the intramolecular cycloaddition using aryne precursor **4a** (Table 1). In the absence of an arynophile, treating **4a** with (trimethylsilylmethyl)magnesium chloride (1.2 equiv) in THF at −78 °C for 1 h provided the desired intramolecular cycloadduct **10a** in moderate yield (Entry 1). The use of *n*-butyllithium or other Grignard reagents returned poorer results, indicating that the silylmethyl Grignard reagent was a suitable activator for this purpose (Entries 2–6). The yield of **10a** was improved when the reaction was performed at higher temperatures (Entries 7–9). The best result was obtained when the reaction was conducted at room temperature for 5 min, which afforded **10a** in excellent yield (Entry 9).[8]

Table 1. Optimization of the reaction conditions



Entry	R–Mtl	Temp./°C	Time	Yield/%
1	Me_3SiCH_2MgCl	−78	1 h	58[a]
2	*n*-BuLi	−78	1 h	24[b]
3	*i*-PrMgCl	−78	1 h	16[b]
4	*i*-PrMgCl·LiCl	−78	1 h	8[b]
5	*n*-BuMgCl	−78	1 h	27[a]
6	PhMgBr	−78	1 h	30[a]
7	Me_3SiCH_2MgCl	−40	1 h	57[b]
8	Me_3SiCH_2MgCl	0	1 h	71[b]
9	Me_3SiCH_2MgCl	rt	5 min	92[a]

[a]Isolated yields. [b]Yields determined by ^{1}H NMR analysis.

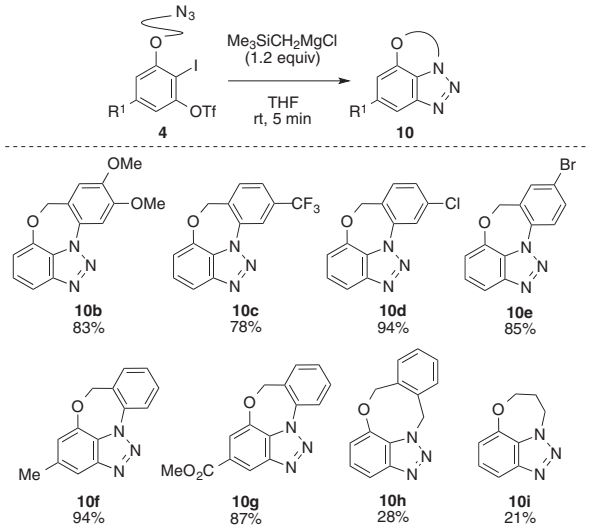
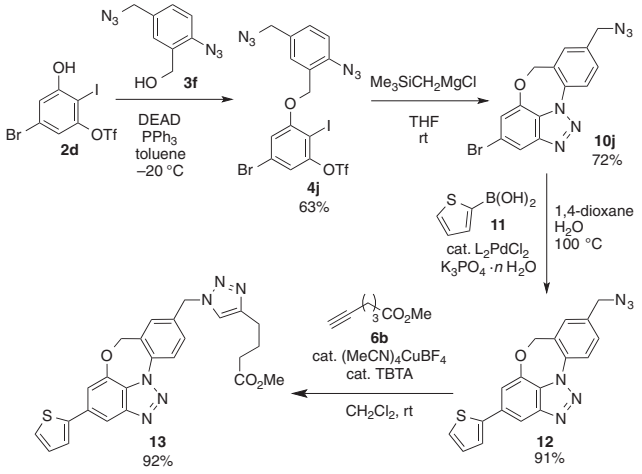


Figure 4. Synthesis of various ring-fused benzotriazoles.

The optimized conditions were applied to the intramolecular cycloadditions of various 3-(azidoalkoxy)arynes generated from precursors **4** (Figure 4).[8] Arynes generated from the precursors bearing electron-rich and -deficient substituents on the azido-substituted benzene rings also participated in the 7-membered ring-forming intramolecular cycloaddition to afford benzotriazoles **10b** and **10c** in high yields. Chloro- and bromo-substituted benzotriazoles **10d** and **10e** were also obtained, efficiently keeping the halogen atoms intact. The presence of an additional methyl or ester group on the 3-alkoxybenzyne ring did not affect the efficacy of intramolecular cycloaddition, to afford **10f** and **10g**, respectively in high yields. Unfortunately, benzotriazole **10h**, which contained a fused 8-membered ring, was only obtained in low yield. In this case, an undesired side-product, formed via an intermolecular reaction, was also obtained. Considering that the yield of benzotriazole **10i**, which does not bear a tethering benzene ring, was also low, the presence of an aromatic azido group must favor this reaction, although the details are yet to be investigated.

The synthesis of a wider range of benzotriazole derivatives was easily achieved using a combination of intramolecular azide–



Scheme 2. Modular synthesis of bistriazole **13** from **2d**, **3f**, **11**, and **6b**.

aryne cycloaddition in conjunction with CuAAC conjugation[9] and Suzuki–Miyaura cross-coupling reaction[10] (Scheme 2). For example, the Mitsunobu reaction between phenol **2d**, bearing a bromo group, and alcohol **3f**, bearing two types of azido groups, afforded aryne precursor **4j**. Treatment of **4j** with the silylmethyl Grignard reagent afforded tetracyclic benzotriazole **10j**, leaving the bromo and azidomethyl groups untouched. These two groups were subsequently coupled with boronic acid **11** and alkyne **6b** to yield bistriazole **13**, which comprises the four module compounds **2d**, **3f**, **11**, and **6b**.[8] This approach enabled the facile preparation of a diverse range of tetracyclic benzotriazoles by substituting the various components with new compounds.

In summary, we have developed a method for the synthesis of new types of benzotriazole derivatives based on the cycloadditions of aryne precursors bearing an azido group. From common starting materials, a diverse range of bis-1,2,3-triazoles were prepared via sequential intermolecular cycloadditions, and unique ring-fused benzotriazoles were obtained via intramolecular azido–aryne cycloaddition. Application of this method to the construction of a unique benzotriazole library is now in progress.

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Supporting Information for characterization of new compounds is available on http://dx.doi.org/10.1246/cl.160349.

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