1,3- and 1,4-Benzdiyne equivalents for regioselective synthesis of polycyclic heterocycles†

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We have devised a novel 1,3-benzdiyne equivalent, capable of quadruple functionalization by sequential benzyne generation and reaction with arynophiles. The key features of this method include the chemoselective generation of two triple bonds in a single benzene ring under fluoride-mediated mild conditions, and the regi ocontrol of each benzyne reaction by the substituent next to the triple bond. This method produced various benzo-fused heteroaromatic compounds via reactions with arynophiles, such as furans, azides, and diazo compounds. A validation of the method is given in the convergent synthesis of the antipsychotic drug risperidone. A similar strategy has also been applied to a 1,4-benzdiyne equivalent to construct linearly benzo-fused heteroaromatics.

Introduction

The reactions of benzyenes with arynophiles are widely utilized for introducing substituents to adjacent carbons of benzene rings.1 The direct installation of fused rings onto benzenes is an advantage specific to the benzyne reaction and is not possible through other methods. Furthermore, a variety of new arynophiles have been recently reported, enriching the diversity of the method.2

The reactions of benzynes, possessing two triple bonds in a single benzene ring, and two arynophiles, would provide a few-step synthesis for the convergent preparation of multifused benzenes. However, benzynes are observed only under gas-phase conditions due to their extreme instability,3 and it would be impossible to react one with two different arynophiles for the synthesis of unsymmetrically fused benzene rings.

An alternative approach is to use benzdiyne equivalents, where two benzenes are generated sequentially in one pot to provide substituted acenes and polycyclic aromatic compounds. If we could control the regiochemistry of consecutive benzyne reactions, starting from benzdiyne equivalents, each with different arynophiles, we could produce a wide range of multi-ring fused unsymmetrical aromatic compounds.4 However, only a limited number of such reactions have been reported, and most of them require several steps for functional group transformations to generate the second benzene.5,6 Therefore, the development of more sophisticated benzdiyne equivalents is needed to facilitate two-step sequential benzyne reactions. Crucial factors in the design of these benzdiyne equivalents include suitable functional groups which enable the generation of the second benzene without further transformations, and a way to control the regiochemistry of each benzyne reaction. The work of Suzuki et al. involving their original 1,4-benzdiyne equivalent meets these requirements, which uses n-butyllithium to generate the benzyenes.6a Very recently, Peña et al. have demonstrated that triple bonds were sequentially generated twice under fluoride-mediated mild conditions from 1,4-benzdiyne equivalents and reacted with two different arynophiles in both stepwise and one-pot manners.7 In contrast, there have been no reports of a suitable 1,3-benzdiyne equivalent.5,8,9

We have attempted sequential benzyne reactions starting from 1,3-benzdiyne equivalents 1, with various arynophiles (Scheme 1). This method was designed to afford unsymmetrically substituted polycyclic aromatic compounds 3, possessing consecutive fused-rings, as are often seen in material and pharmaceutical science.10 While compounds like 3 have been

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**Scheme 1** Design of benzdiyne equivalent 1 that can sequentially generate two triple bonds in a single benzene ring and control the regiochemistry of two benzyne reactions by the substituents next to each triple bond.
mainly synthesized via linear, multi-step routes, our approach is convergent and rapid, proceeding by the combination of 1 and two different arynes (I and II), and allows a rational design for the production of a library of compounds. We were particularly interested in its application to the synthesis of benzofused heterocycles for medicinal chemistry. Therefore, we planned reactions using heteroatomic 1,3-dipoles, such as azides, nitrones, diazo compounds, and nitrile oxides, as the arynes.

We aimed to develop a synthetic methodology in which (1) two benzyne (4 and 5) are chemoselectively generated in a stepwise manner without any additional functionalization steps, (2) each benzyne is generated under mild conditions using a fluoride, and (3) the two cycloaddition reactions of 4 and 5 with 1 and II proceed in a highly regioselective manner (Scheme 1). In this article, we report the preparation of a new 1,3-benzdiyne equivalent 1b [SiR3 = Si(t-Bu)Me2], and a method for the preparation of unsymmetrical, angular, and multi-ring fused heterocyclic compounds 3, which satisfies the above criteria. One significant advantage of this method is the high regioselectivity of both benzyne reactions, in which the first step is controlled by the traceless directing group, R3Si (ref. 11) of 4, and the second step by the cyclic systems13 of 5.

**Results and discussion**

We synthesized two 1,3-benzdiyne equivalents, 1a and 1b, which were treated with CsF in the presence of 2,4-dimethylfuran 6a. The reaction of 1a with 6a produced the undesired cycloaddition product 8 via benzyne 7 (Scheme 2). However, the reaction of 1b afforded the desired cycloaddition product 10a (78% yield) through the Diels–Alder reaction of the expected benzyne 4a with 6a. An important observation is that the double cycloaddition product 3a was not detected by GC analysis of the crude reaction mixture after 30 min (see ESI†). This may be due to the lower reactivity of the Me2(t-Bu)Si group, even in the presence of excess CsF and 6a. The generation of the second benzyne 5a was achieved after long reaction time (19 h) under the same reaction conditions using CsF to give 3a in 90% isolated yield.

We attempted to synthesize compounds 3b–f through stepwise benzyne cycloaddition reactions from 1b (Table 1). All reactions of 3-silylbenzynes 4a with arynes 6b–e provided cycloaddition products 10 with good regioselectivities due to synergetic effect of the neighboring Me2(t-Bu)Si (ref. 11) and the distant triflyloxy (TfO) groups. Among them, unexpected proximal regioselectivity (proximal-10d : distal-10d = 78 : 22) was observed in the reaction between 3-silylbenzene 4a and nitrone 6d (entry 4–1), which was opposite to the previously reported reactions of 3-silylbenzenes with nitrones (for structural determinations, see ESI†). This result is probably due to the inductively electron-withdrawing effect of the TfO group at C4. This reaction of 4a with sydnone 6e to give distal-2H-indazole 10e (entry 5–1) is particularly noteworthy, as the reactions of unsymmetrical benzenes such as 3-methoxynbenzene with sydrones have been reported to afford mixtures of regioisomers in 1 : 1 ratio. The reaction of benzenes 5 with arynes 6f and 6g provided polycyclic compounds 3b–f. This is the first report of the generation and reaction of 4,5-benzotriazolylne 5b (entry 2–2), 6,7-benzisoxazolynne 5c (entry 3–2), 4,5-benzisoxazolynne 5d (entry 4–2), and 6,7-2H-indazolynne 5e (entry 5–2). The regioselectivity of these reactions is higher than that of sterically similar 4,5-indolynne (see preliminary theoretical discussion of these regioselectivities in ESI†).

Next, one-pot sequential benzyne cycloadditions from 1b were demonstrated for the synthesis of angular tricyclic heterocycles 3 without isolating 10 (Scheme 3). After a mixture of 1b (1.0 equiv.), benzyl azide 6b (1.1 equiv.) and CsF (4.0 equiv.) in MeCN was stirred at room temperature for 30 min, 2-methylfuran 6h (3.0 equiv.) and 18-crown-6 (4.0 equiv.) were added and then the reaction mixture was stirred for 16 h at 0 °C (Scheme 3–1). Gratifyingly, proximal-3g was obtained as a major product (proximal-3g : distal-3g = 63 : 37, total 56%). The tricyclic compound, distal-3e was also synthesized as the predominant product (distal-3c : proximal-3c = 93 : 7, total 38%) by a similar one-pot combination of arynes, nitrone 6d and 6b (Scheme 3–2). The yield and regioselectivity of these products were comparable to those obtained by the stepwise method (Table 1, entries 4–1 and 4–2).

We applied these findings to the convergent synthesis of the antipsychotic drug risperidone 14 (Scheme 4). The silylbenzene 4a and a nitrile oxide 6i (ref. 2e) were simultaneously generated

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**Scheme 2** Sequential benzyne generation from benzodiyne equivalents 1a and 1b followed by Diels–Alder reaction with furan 6a.
from a mixture of 1b and a chloro-oxime 11 and then reacted in situ to form distal-10f as a single regioisomer. The next reaction of 6,7-benzisoxazolyne 5f, generated by BnMe3NF (ref. 14 and 15) and a fluoride 6j, provided 3h with excellent regioselectivity. Finally, the synthesis was completed by the N-deprotection of 3h to give 12 and the alkylation with 13. This result suggests that 1b should be useful tool for the expeditious divergent synthesis of a wide variety of biologically active compounds and their derivatives by choosing different aryphiles once 1b become easily available (for the first synthesis of 1b, see ESI†).

We also report the synthesis of linearly fused, unsymmetrical polycyclic aromatics 19 using 15 (ref. 17–19) as a 1,4-benzdiyne equivalent (Table 2). The first benzyne generation proceeds using CsF at room temperature in MeCN for a short time, under which conditions, generation of the second benzyne does not occur (see ESI†). The mono-cycloaddition products 17, obtained as a mixture of two regioisomers, were subjected to the second reaction with aryphiles II, without separation of the regioisomers,16 to afford the multicyclic compounds 19. Due to the dual effect of the TfO group14 and Me3Si group15 of 16, the all first benzyne reactions proceeded in a regioselective manner.
beyond expectation (Table 2, entries 1-1, 2-1 and 3-1), although these selectivities were only a little lower than those of the 1,3-benzdiyne equivalent $1b$ (see, Table 1). Interestingly, the second benzyn reactions also regioselectively provided cycloaddition products $19$ probably because of the inductive effect of heteroatoms such as nitrogen and oxygen constructing heterocycles (entries 2-2 and 3-2). These results provide useful information for regioselectivity control of benzyn cycloadditions from distant positions. Importantly, the one-pot synthesis of a linear tricyclic compound $19a$ from $15$, $6b$ and $6l$ was also successfully achieved (see entry 1-2).

Conclusions

In conclusion, we have developed a novel synthetic route to multi-ring fused heterocycles by the combination of benzdiyne equivalents and arynophiles. In this study, the newly generatedazole-fused benzenes were found to exhibit higher regioselectivities than those of sterically similar 4,5-indolyne.$^{12a}$ This method has facilitated the convergent synthesis of the antipsychotic risperidone. Therefore, we believe that this synthetic methodology will be invaluable to drug discovery. Work is ongoing into easier, scalable synthetic methods for these benzdiyne equivalents,$^{19}$ analysis of the origin of the regioselectivity (see ESI†), and applications to medicinal chemistry.

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For unique 3- or 4-TFO group-directed benzene reactions, see: (a) T. Ikawa, H. Kaneko, S. Masuda, E. Ishitsubo, H. Tokiwa and S. Akai, *Organometallics*, 2015, 13, 520;
The use of BnMe₃NF as an anhydrous fluoride source was necessary both for the benzyne generation and for the nucleophilic addition of the fluoride because a significant amount of the phenol derivative was formed when Bu₄NF·(t-BuOH)₄ was used. The latter results are probably owing to the nucleophilic addition of contaminant water to generate benzyne 5f.¹⁵


2,4-Bis(trimethylsilyl)-1,3-bis(trifluoromethanesulfonyloxy)benzene 15 has been recognized as a one-step 1,4-benzdiyne equivalent that consecutively generates two triple bonds at the C1 and C4 positions of a single benzene to react with two equivalents of a single arynophile.⁴,¹⁸ Peña et al. have recently used 15 as a quasi-step-by-step benzdiyne equivalent for the synthesis of polyaromatic hydrocarbon (PAH), in which the second benzyne was not generated because of the precipitation of the mono-cycloaddition product.¹⁸

We have developed an improved, 3-step synthesis of 15 with 70% overall yield, while the reported method required 4 steps and gave 13% overall yield.¹⁸ Recently, another improved method was reported which required 3 steps in 59% overall yield (see ESI†).

Both regioisomers 17 should be transformed to the same benzenes 18.