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

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We have devised a novel 1,3-benzydiyne 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 regiocontrol 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-benzydiyne equivalent to construct linearly benzo-fused heteroaromatics.

Introduction

The reactions of benzyynes with arynophiles are widely utilized for introducing substituents to adjacent carbons of benzene rings.† 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.‡

The reactions of benzydines, 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, benzydines are observed only under gas-phase conditions due to their extreme instability,§ 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 benzydiyne 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 benzydiyne equivalents, each with different arynophiles, we could produce a wide range of multiring fused unsymmetrical aromatic compounds.¶ 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 benzyne.¶,† The development of more sophisticated benzydiyne equivalents is needed to facilitate two-step sequential benzyne reactions. Crucial factors in the design of these benzydiyne equivalents include suitable functional groups which enable the generation of the second benzyne 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-benzydiyne equivalent meets these requirements, which uses n-butyllithium to generate the benzyynes.† Very recently, Peña et al. have demonstrated that triple bonds were sequentially generated twice under fluoride-mediated mild conditions from 1,4-benzydiyne equivalents and reacted with two different arynophiles in both stepwise and one-pot manners.¶ In contrast, there have been no reports of a suitable 1,3-benzydiyne equivalent.¶,†,∥

We have attempted sequential benzyne reactions starting from 1,3-benzydiyne 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.† The compounds like 3 have been

Scheme 1 Design of benzydiyne 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 benzo-fused 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 benzenes (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 I 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 [SiR$_3$ = Si(t-Bu)Me$_2$], 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, R$_{3}$Si (ref. 11) of 4, and the second step by the cyclic systems$^{13}$ 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-dimethylyfuran 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 Me$_2$(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-silylbenzyne 4a with arynes 6b–e provided cycloaddition products 10 with good regioselectivities due to the synergistic effect of the neighboring Me$_2$(t-Bu)Si (ref. 11f) and the distant triflyoxy (TfO) groups.$^{13}$ Among them, unexpected proximal regioselectivity (proximal-10d: distal-10d = 78:22) was observed in the reaction between 3-silylbenzyne 4a and nitrone 6d (entry 4-1), which was opposite to the previously reported reactions of 3-silylbenzynes with nitrones (for structural determinations, see ESI†).$^{14}$ This result is probably due to the inductively electron-withdrawing effect of the TfO group at C4.$^{15}$ The reaction of 4a with syndone 6e to give distal-2H-indazole 10e selectively (entry 5-1) is particularly noteworthy, as the reactions of unsymmetrical benzyne such as 3-methoxybenzyne with syndones have been reported to afford mixtures of regioisomers in 1:1 ratio.$^{16}$ The reaction of benzyne 5 with arynes 6f and 6g provided polycyclic compounds 3b–f. This is the first report of the generation and reaction of 4,5-benzotriazolone 5b (entry 2-2), 6,7-benzoisoxazolone 5c (entry 3-2), 4,5-benzoxazolylamine 5d (entry 4-2), and 6,7,2H-indazolone 5e (entry 5-2). The regioselectivity of these reactions is higher than that of sterically similar 4,5-indolone (see preliminary theoretical discussion of these regioselectivities in ESI†).$^{12a,b}$ The reactions of 5c with 6b and 5e with 6g provided distal-3d and proximal-3f exclusively (entries 3-2 and 5-2).

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 main product (proximal-3g: distal-3g = 63:37, total 56%). The tricyclic compound, distal-3e was also synthesized as the predominant product (distal-3e: proximal-3e = 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.

Scheme 2 Sequential benzyne generation from benzdiyne 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 arynophiles 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 arynophiles II, without separation of the regioisomers, to afford the multicyclic compounds 19. Due to the dual effect of the TIO group14 and Me3Si group15 of 16, the all first benzyne reactions proceeded in a regioselective manner.

**Table 1  Reactions of 1b with two different arynophiles 6 for the synthesis of angular polycycles 3**

<table>
<thead>
<tr>
<th>Entry</th>
<th>Arynophile I</th>
<th>Major Isomer</th>
<th>Regioselectivity</th>
<th>Yield</th>
<th>Entry</th>
<th>Arynophile II</th>
<th>2nd benzyne 5</th>
<th>Major Isomer</th>
<th>Regioselectivity</th>
<th>Yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>1-1</td>
<td>6a</td>
<td>10a</td>
<td>—</td>
<td>78%</td>
<td>1-2</td>
<td>BnN3</td>
<td>5a</td>
<td>distal-3b</td>
<td>87 : 13</td>
<td>63%</td>
</tr>
<tr>
<td>2-1</td>
<td>6b</td>
<td></td>
<td>98 : 2</td>
<td>79%</td>
<td>2-2</td>
<td>6f</td>
<td>5b</td>
<td>proximal-3c</td>
<td>76 : 24</td>
<td>89%</td>
</tr>
<tr>
<td>3-1</td>
<td>Mes=N−O</td>
<td>distal-10c</td>
<td>89 : 11</td>
<td>55%</td>
<td>3-2</td>
<td>6b</td>
<td>5c</td>
<td>distal-3d</td>
<td>&gt;98 : 2</td>
<td>74%</td>
</tr>
<tr>
<td>4-1</td>
<td>6d</td>
<td>proximal-10d</td>
<td>78 : 22</td>
<td>68%</td>
<td>4-2</td>
<td>6b</td>
<td>5d</td>
<td>distal-3e</td>
<td>86 : 14</td>
<td>71%</td>
</tr>
<tr>
<td>5-1</td>
<td>6e</td>
<td>distal-10e</td>
<td>85 : 15</td>
<td>49%</td>
<td>5-2</td>
<td>6g</td>
<td>proximal-3f</td>
<td>&gt;98 : 2</td>
<td>58%</td>
<td></td>
</tr>
</tbody>
</table>

| **Scheme 3** | One-pot synthesis of unsymmetrical angular heterocycles 3g and 3e. |

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Conditions: 1b or 10 (1.0 equiv.), arynophile (3.0 equiv.), CsF (3.0 equiv.) in MeCN at rt. The ratio of major and minor products was determined by 1H NMR. Total isolated yield of distal-10 (or distal-3) and its regioisomer proximal-10 (or proximal-3). Mes = C6H2-2,4,6-Me3.
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 benzyne reactions also regioselectively provided cycloaddition products 19 probably because of the inductive effect of hetero-atoms such as nitrogen and oxygen constructing heterocycles (entries 2-2 and 3-2). These results provide useful information for regioselectivity control of benzyne 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. 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, analysis of the origin of the regioselectivity (see ESI†), and applications to medicinal chemistry.

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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.⁴¹⁸ 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 benzine was not generated because of the precipitation of the mono-cycloaddition product²⁻⁴.

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.¹⁹ 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 benzynes 18.