Accepted Article

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This manuscript has been accepted after peer review and appears as an Accepted Article online prior to editing, proofing, and formal publication of the final Version of Record (VoR). This work is currently citable by using the Digital Object Identifier (DOI) given below. The VoR will be published online in Early View as soon as possible and may be different to this Accepted Article as a result of editing. Readers should obtain the VoR from the journal website shown below when it is published to ensure accuracy of information. The authors are responsible for the content of this Accepted Article.

To be cited as: *Eur. J. Org. Chem.* 10.1002/ejoc.201900570

Link to VoR: <http://dx.doi.org/10.1002/ejoc.201900570>

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A Ring Expansion Route to Benzofused *N*-Heterocycles via Aryne Insertion into 1,3-Diaza-heterocycles

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Abstract: Arynes have been found to undergo formal σ -bond insertion into a C(sp³)-N bond for the first time. This transformation is utilized in the ring expansion of 1,3-diaza-heterocycles to afford benzofused medium-ring *N*-heterocycles in a single step. This represents a novel route to biologically relevant 2,3,4,5-tetrahydro-1*H*-benzo[*e*][1,4]diazepines, prepared directly from easily accessible imidazolidines. An example of the ring expansion of a 1,3-diazetidine is also reported, which affords the corresponding 1,2,3,4-tetrahydroquinazoline.

Introduction

Arynes are versatile reactive intermediates that facilitate the rapid generation of molecular complexity.¹ The advent of aryne precursors that act under mild conditions, such as *o*-silylaryl triflates² and the hexadehydro-Diels-Alder (HDDA) reaction of polyalkynyl substrates,^{1,3} has led to a recent resurgence in the development of novel reactivity. One particularly valuable area of aryne chemistry is the formal insertion of the arene motif into a wide range of σ - and π -bonds, including carbon-carbon, carbon-heteroatom and heteroatom-heteroatom bonds.⁴ The transformations typically occur under mild conditions without the need for additional Lewis acid or transition metal reagents and generate useful poly-functionalized aromatic products.⁵ For example, biologically active heterocycles and *o*-functionalized aniline derivatives – key building blocks for synthesis – have been accessed via aryne insertion into the C(sp²)-N bond of ureas,⁶ amides⁷ and imides^{7b,8} (Scheme 1A).⁹ These transformations are understood to proceed via initial *N*-arylation of **1**, affording zwitterion **2** that undergoes subsequent intramolecular nucleophilic substitution at the carbonyl carbon, via azetidinium **3**, to furnish the insertion products **4**.

Given our interests in the development of new aryne-based methodology,¹⁰ we envisaged a related approach to the synthesis of biologically relevant *N*-heterocycles via the formal insertion of an aryne into a C(sp³)-N σ -bond of 1,3-diaza-heterocycles **5** (Scheme 1B). It was proposed that *N*-arylation would generate zwitterionic intermediate **6**, which should be in equilibrium¹¹ with the ring-opened form **7** that could undergo intramolecular cyclization to reveal the ring-expanded benzofused *N*-heterocycle **8**. For example, employing readily accessible 1,3-imidazolidines (**5**, *n* = 1) would reveal a new route to biologically active 1,4-benzodiazepines (**8**, *n* = 1), one of the most widely used heterocycles in medicinal chemistry.¹² These privileged scaffolds are employed as sedatives,

anticonvulsants,¹³ platelet-activating factor antagonists,¹⁴ human immunodeficiency virus (HIV) transactivator Tat antagonists¹⁵ and reverse transcriptase inhibitors.¹⁶

A) C(sp²)-N σ -bond insertion: ureas⁶ & amides⁷

B) C(sp³)-N σ -bond insertion: 1,3-diaza-heterocycles - this work

Scheme 1. Aryne insertion into C-N σ -bonds.

Existing methods to synthesize 1,4-benzodiazepines are typically multistep processes.¹⁷ These include cyclization of *o*-halobenzoic acid derivatives with 1,2-ethylenediamines,¹⁸ *o*-amino-methylanilines with bis-electrophiles,¹⁹ *o*-aminobenzophenones with α -amino acid derivatives²⁰ and the Pictet-Spengler reaction of *N*-phenyl-1,2-ethylenediamines.²¹ Herein we report the development of a new direct route to the synthesis of 2,3,4,5-tetrahydrobenzo-1,4-diazepines that operates via a ring expansion of readily accessible 1,3-diaza-heterocycles. This approach showcases the first examples of a formal aryne insertion into a C(sp³)-N σ -bond.

Results and Discussion

In order to test our hypothesis of a formal insertion of benzyne into an amina C-N σ -bond, 1,3-diphenylimidazolidine **9** was exposed to 2-trimethylsilylphenyl triflate **10a** under a variety of aryne-forming conditions (see Table 1 for selected optimization studies).²² Pleasingly, initial attempts using CsF in acetonitrile furnished the C-N insertion product, 2,3,4,5-tetrahydrobenzodiazepine **11a**, as the major product in good yield after 4 hours (entry 1). Interestingly, mono-arylated linear 1,2-ethylenediamine **12** and the bis-arylated analogue **13** were

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also identified; both by-products involving ring-opening of the imidazolidine ring and loss of the C-2 methylene group. Evaluation of a range of common activators for *o*-silylaryl triflate precursors identified CsF as the most promising reagent (entries 1-7) and revealed that the precise distribution between the ring-expanded (**11a**) and ring-opened (**12** and **13**) products was extremely dependent upon the reaction conditions.²³ Increasing the temperature to 80 °C led to more by-product formation (entry 8), whereas mainly unreacted imidazolidine **9** was recovered when the temperature was lowered to 30 °C (entry 9). A small increase in benzyne precursor (1.2 equivalents) resulted in more bis-arylated diamine **13** (entry 10). Optimal concentration was found to be 0.1 M, as both higher and lower dilutions caused a drop in the insertion:linear product ratios (entry 1 vs entries 11 and 12). Considering the proposed mechanism for C-N insertion (see Scheme 1B), it followed that undesired protonation of the intermediate aryl anion (**6** or **7**) would prohibit cyclization to the benzodiazepine and instead favour ring-opening and hydrolysis.²⁴ As such, attempts were made to remove trace water (4 Å molecular sieves, entry 13) as well as changing from

acetonitrile to ethereal solvents^{10c} (DME, entry 14; THF, entries 3 and 6); however, all changes resulted in less C-N insertion. Finally, the addition of transition metal salts such as CuI and AgI (entries 15 and 16) – proposed to stabilize the aryl anion²⁵ and thereby favour cyclization – did not improve the reaction. In the case of CuI this led to a significant reduction in conversion, potentially caused by the imidazolidine binding to the Cu.

With optimized conditions in hand for the formal insertion of benzyne into a C(sp³)-N bond of 1,3-diphenylimidazolidine **9** (entry 1, Table 1), we began to explore the scope of the ring expansion reaction. Pleasingly, tetrahydrobenzodiazepines **11a-h** were furnished in moderate to good yields when *N,N*-diphenylimidazolidine **9** was exposed to a range of substituted aryne precursors **10a-h** (Scheme 2). It is noteworthy that longer reaction times were required for arynes **10b-h** (16 h) in comparison to benzyne **10a** (4 h), although identical results were achieved when **10a** was also left for 16 h. The transformation was equally tolerant of arynes substituted with electron-donating (methylenedioxy, **10b**, 3,4-dimethyl, **10c**, cyclopentyl, **10e**, 3-methoxy, **10f**, 5-methyl, **10h**) or electron-withdrawing groups (3,4-difluoro, **10d**, 5-fluoro, **10g**). Interestingly, benzodiazepines bearing alkyl or fluoro substituents (**10c-e** and **10g-h**) were found to be unstable to purification by flash column chromatography. As a result, the crude reaction mixtures were treated with trifluoromethanesulfonic acid (TfOH) to generate the corresponding triflate salts, which subsequently proved amenable to chromatographic purification. Treatment of imidazolidine **9** with unsymmetrical arynes led to regioisomeric mixtures of the corresponding benzodiazepine products. The 3-methoxy aryne derivative **10f** gave a 3:1 mixture of the 6- and 9-methoxy-1,2,3,4-tetrahydrobenzodiazepines **11f**. Similarly, the 5-fluoro derivative **10g** afforded a 3:1 preference for the 7-fluoro product. Finally, the less polarized 5-methyl-substituted aryne led to a 1:1 regioisomeric mixture of **11h**. These observations are consistent with initial nucleophilic attack of nitrogen at the distal site of the aryne, resulting in an aryl anion that is stabilized by the adjacent electron-withdrawing substituent.

The reaction was found to be amenable to different *N*-substituted imidazolidines, as both electron-withdrawing (Boc, **14**; CO₂Me, **15**) and electron-donating groups (Me, **16**) provided tetrahydrobenzodiazepines **24-26** in low to moderate yields over 16 hours (Scheme 3).²⁶ Symmetrical 1,3-dimethylimidazolidine **20** proved to be too electron-rich, affording solely the linear 1,2-ethylenediamine products; the same outcome as when a substituent was introduced at C-2 of the imidazolidine ring (**21**). Conversely, the electron-poor 1,3-di-Boc-imidazolidine **22** and 1,3-diphenylbenzimidazolidine **23** led to complete recovery of starting material. However, switching to a more electron-donating *para*-methoxy phenyl (PMP) group on nitrogen (**17**) led to the corresponding dibenzodiazepine **27** in moderate yield. Finally, preliminary studies revealed that aryne insertion is not limited to imidazolidine derivatives. For example, treating 1,3-diphenyl-1,3-diazetidene **18** with benzyne precursor **10a** at 35 °C led to the corresponding 1,2,3,4-tetrahydroquinazoline **28**. Furthermore, linear *N,N*-dimethyl-*N,N*-diphenylmethanediamine **19** also underwent formal aryne insertion, affording the aminomethylaniline **29** in low yield.

A mechanism for the formation of tetrahydrobenzodiazepines and the observed by-products is

Table 1. Selected optimization studies for benzyne insertion into *N,N*-diphenylimidazolidine **9**.

Entry	Activator ^a	Additive ^b	Solvent	T (°C)	Yield ^c (%)			
					9	11	12	13
1	CsF	–	CH ₃ CN	50	5	55	25	10
2	CsF	18-c-6	CH ₃ CN	50	12	45	18	15
3	TBAF ^d	–	THF	50	5	5	65	10
4	TBAT	–	CH ₃ CN	50	7	5	67	7
5	KF	18-c-6	CH ₃ CN	50	29	10	10	35
6	KF	18-c-6	THF	50	22	42	26	9
7	Cs ₂ CO ₃	18-c-6	CH ₃ CN	50	10	26	47	10
8	CsF	–	CH ₃ CN	80	12	25	40	16
9	CsF	–	CH ₃ CN	30	60	20	5	0
10 ^e	CsF	–	CH ₃ CN	50	5	50	20	15
11	CsF	–	CH ₃ CN ^f	50	20	42	30	9
12	CsF	–	CH ₃ CN ^g	50	10	34	39	8
13	CsF	4Å MS	CH ₃ CN	50	6	25	40	15
14 ^h	CsF	–	DME	50	70	8	10	4
15	CsF	CuI ⁱ	CH ₃ CN	50	52	27	18	3
16	CsF	AgI ⁱ	CH ₃ CN	50	16	50	23	4

[a] 3 equiv. activator. [b] 3 equiv. additive. [c] ¹H NMR yield vs dibromomethane internal standard. [d] 1.0 M in THF. [e] 1.2 equiv. benzyne **10a** and 3.6 equiv. CsF. [f] 0.01 M. [g] 0.5 M. [h] reaction left for 24 h until all benzyne **10a** consumed. [i] 0.2 equiv additive. TBAT = tetrabutylammonium triphenyldifluorosilicate. MS = molecular sieve.

Scheme 2. Scope of C-N insertion with different aryne derivatives. ^a ¹H NMR yield vs dibromomethane internal standard, isolated yields in parentheses. ^b 4 h. ^c Isolated as HOTf salt. ^d 1.5 equiv. aryne precursor. ^e ratio determined by analysis of ¹H NMR spectrum of crude mixture.

Scheme 3. Scope of C-N insertion with different imidazolidine derivatives. ^a ¹H NMR yield vs dibromomethane internal standard, isolated yields in parentheses. ^b 35 °C. ^c 4 h. PMP = *para*-methoxyphenyl.

proposed in Scheme 4. Initial nucleophilic attack of nitrogen onto the aryne affords zwitterion **30** that is in equilibrium with the ring-opened form **31**. A 7-*endo-trig* cyclization of **31** furnishes **11a** and completes the formal insertion reaction. However, in the presence of trace water, deleterious protonation of either **30** or **31**, followed by hydrolysis, results in loss of the C-2 methylene

group and formation of mono-arylated ethylenediamine **12**. Further arylation with another equivalent of aryne leads to **13**.

Scheme 4. Proposed mechanism for the formation of the major products observed during aryne insertion reactions into 1,3-diaza-heterocycles.

Conclusions

The formal insertion of an aryne into a C(sp³)-N bond has been achieved for the first time. This has been applied to the preparation of a number of tetrahydro-1,4-benzodiazepine scaffolds, accessed via a novel ring-expansion of readily accessible imidazolidines with a range of substituted aryne derivatives. Overcoming competitive formation of linear 1,2-ethylenediamine by-products proved a challenge for the methodology and accounted for the moderate yields of the insertion products obtained. Encouraging preliminary investigations in our laboratory have demonstrated that alternative 1,3-diazo-substrates also undergo formal aryne insertion and investigations are currently underway to evaluate the general applicability of this approach.

Acknowledgments

We are grateful to the EPSRC (EP/M026221/1, C.R.J.) and the China Scholarship Council (Y.Y.) for financial support. We also thank the EPSRC UK National Mass Spectrometry Facility at Swansea University.

Keywords: arynes • N-heterocycles • insertion • ring expansion • tetrahydro-1,4-benzodiazepine

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