EurJOC
European Journal of Organic Chemistry

A Journal of
ChemPubSoc Europe

Accepted Article

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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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10.1002/ejoc.201900570

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

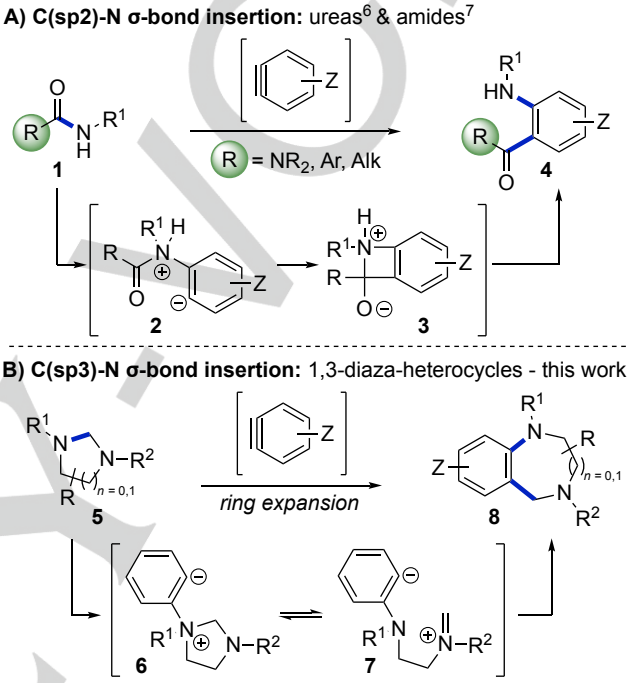
Yun Yang,[a] Yue Xu,[a] and Christopher R. Jones*[a]

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 triflates[2] and the hexadehydro-Diels-Alder (HDDA) reaction of polyalkynyl substrates,[1j,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] amides[7] 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 equilibrium[11] 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 antagonists[15] and reverse transcriptase inhibitors.[16]



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 derivatives[20] 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 aminal 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 acetontrile 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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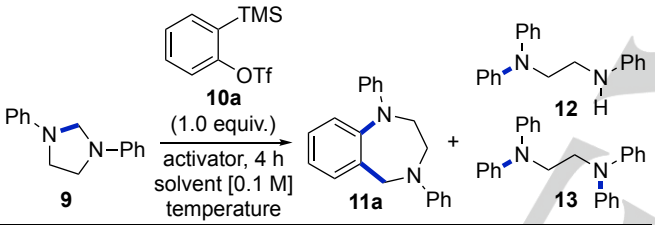
also identified; both by-products involving ring-opening of the imidazolidine ring and loss of the C-2 methylene group. Evaluation of a range of common activators for *o*-silylaryl triflate precursors identified CsF as the most promising reagent (entries 1-7) and revealed that the precise distribution 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

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



Entry	Activator[a]	Additive[b]	Solvent	T (˚C)	Yield[c] (%)			
					9	**11**	**12**	**13**
1	CsF	–	CH_3CN	50	5	55	25	10
2	CsF	18-c-6	CH_3CN	50	12	45	18	15
3	TBAF[d]	–	THF	50	5	5	65	10
4	TBAT	–	CH_3CN	50	7	5	67	7
5	KF	18-c-6	CH_3CN	50	29	10	10	35
6	KF	18-c-6	THF	50	22	42	26	9
7	Cs_2CO_3	18-c-6	CH_3CN	50	10	26	47	10
8	CsF	–	CH_3CN	80	12	25	40	16
9	CsF	–	CH_3CN	30	60	20	5	0
10[e]	CsF	–	CH_3CN	50	5	50	20	15
11	CsF	–	CH_3CN[f]	50	20	42	30	9
12	CsF	–	CH_3CN[g]	50	10	34	39	8
13	CsF	4Å MS	CH_3CN	50	6	25	40	15
14[h]	CsF	–	DME	50	70	8	10	4
15	CsF	CuI[i]	CH_3CN	50	52	27	18	3
16	CsF	AgI[i]	CH_3CN	50	16	50	23	4

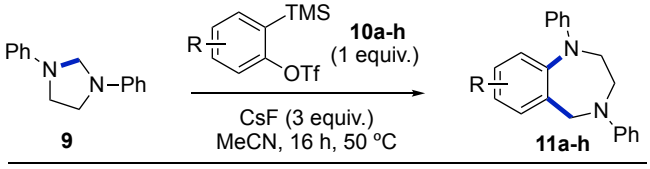
[a] 3 equiv. activator. [b] 3 equiv. additive. [c] ^{1}H NMR yield *vs* dibromomethane internal standard. [d] 1.0 M in THF. [e] 1.2 equiv. benzyne **10a** and 3.6 equiv. CsF. [f] 0.01 M. [g] 0.5 M. [h] reaction left for 24 h until all benzyne **10a** consumed. [i] 0.2 equiv additive. TBAT = tetrabutylammonium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

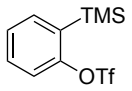
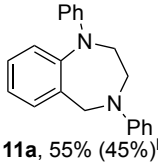
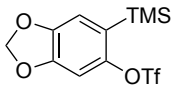
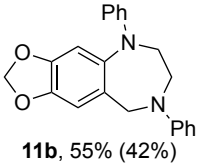
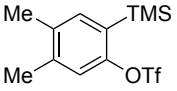
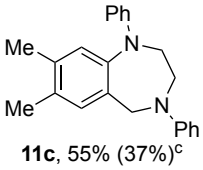
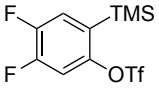
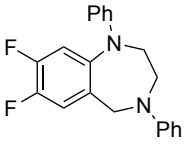
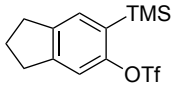
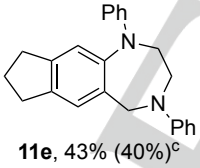
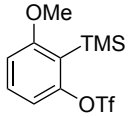
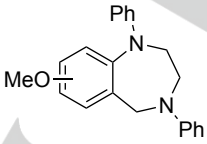
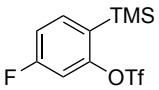
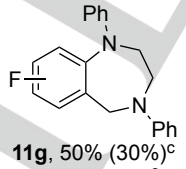
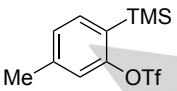
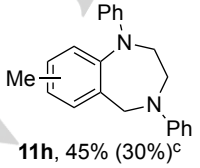
acetonitrile to ethereal solvents[10c] (DME, entry 14; THF, entries 3 and 6); however, all changes resulted in less C-N insertion. Finally, the addition of transition metal salts such as CuI and AgI (entries 15 and 16) – proposed to stabilize the aryl anion[25] and thereby favour cyclization – did not 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.

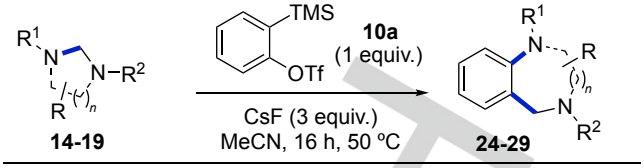
The reaction was found to be amenable to different *N*-substituted imidazolidines, as both electron-withdrawing (Boc, **14**; CO_2Me, **15**) and electron-donating groups (Me, **16**) provided tetrahydrobenzodiazepines **24**-**26** in low to moderate yields over 16 hours (Scheme 3).[26] Symmetrical 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-diazetidine **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.

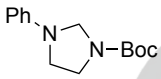
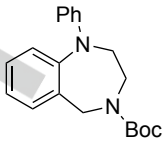
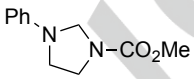
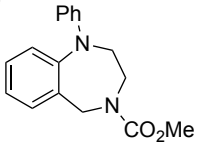
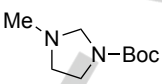
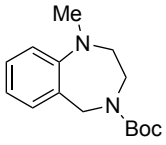
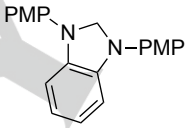
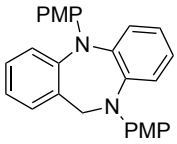
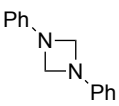
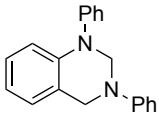
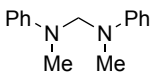
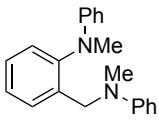
A mechanism for the formation of tetrahydrobenzodiazepines and the observed by-products is



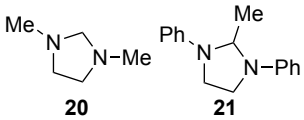
aryne	product[a]
 **10a**	 **11a**, 55% (45%)[b]
 **10b**	 **11b**, 55% (42%)
 **10c**	 **11c**, 55% (37%)[c]
 **10d**[d]	 **11d**, 40% (35%)[c]
 **10e**	 **11e**, 43% (40%)[c]
 **10f**	 **11f**, 47% (40%) 6- / 9-OMe = 3:1[e]
 **10g**[d]	 **11g**, 50% (30%)[c] 7- / 8-F = 3:1[e]
 **10h**	 **11h**, 45% (30%)[c] 7- / 8-Me = 1:1[e]

Scheme 2. Scope of C-N insertion with different aryne derivatives. [a] ^{1}H 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 ^{1}H NMR spectrum of crude mixture.



1,3-diamine	product[a]
 **14**	 **24**, 40% (20%)
 **15**	 **25**, 10% (6%)
 **16**	 **26**, 50% (34%)
 **17**	 **27**, 40% (30%)
 **18**	 **28**, 15% (11%)[b]
 **19**	 **29**, 28% (10%)[c]

Unsuccessful substrates:



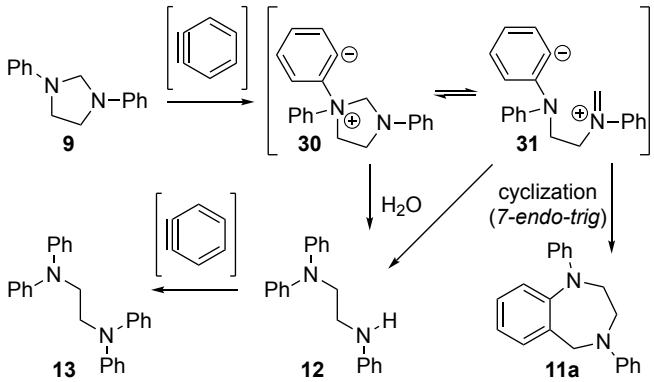
20 **21** **22** **23**

linear 1,2-diamine products *recovered starting material*

Scheme 3. Scope of C-N insertion with different imidazolidine derivatives. [a] ^{1}H 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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