JACS
JOURNAL OF THE AMERICAN CHEMICAL SOCIETY

Communication

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Generation and Regioselective Trapping of a 3,4-Piperidyne for the Synthesis of Functionalized Heterocycles

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Supporting Information

ABSTRACT: We report the generation of the first 3,4-piperidyne and its use as a building block for the synthesis of annulated piperidines. Experimental and computational studies of this intermediate are disclosed, along with comparisons to the well-known 3,4-pyridyne. The distortion/interaction model is used to explain the observed regioselectivities.

Heterocycles containing one or more nitrogen atoms constitute nearly 60% of all small-molecule drugs that have been approved by the U.S. Food and Drug Administration.[1] The most prevalent *N*-containing heterocycle is the piperidine ring, which is found in 72 currently marketed small-molecule drugs. Notable examples include the blockbuster drugs clopidogrel (Plavix), tadalafil (Cialis), and solifenacin (VESIcare) (Figure 1). In view of the importance of this medicinally privileged scaffold, new methods to rapidly access annulated piperidines from simple precursors are highly sought after.

With the aim of developing a new method for the synthesis of decorated piperidines, we questioned whether the unusual 3,4-piperidyne intermediate **1** (Figure 1) could be generated and used as a new synthetic building block. Notably, 3,4-piperidynes have never been accessed previously. The most closely related studies have involved the isomeric 2,3-piperidyne **2**, which has been the subject of two seminal investigations. In 1988, Wentrup and co-workers generated **2** (R = H) using flash vacuum pyrolysis.[2] Although **2** was deemed unstable above −150 °C and was never utilized in any synthetic application, Wentrup's studies validated the notion that **2** could be generated. Additionally, during the preparation of this communication, Danheiser disclosed an efficient means to access **2** (R = Ts) and performed a series of synthetically useful trapping reactions.[3] Interestingly, whereas piperidynes have been rarely studied,[4] the corresponding aromatic pyridynes **3**[5] and **4**,[6] along with many other arynes and hetarynes, have been widely pursued for more than half a century.[7−9]

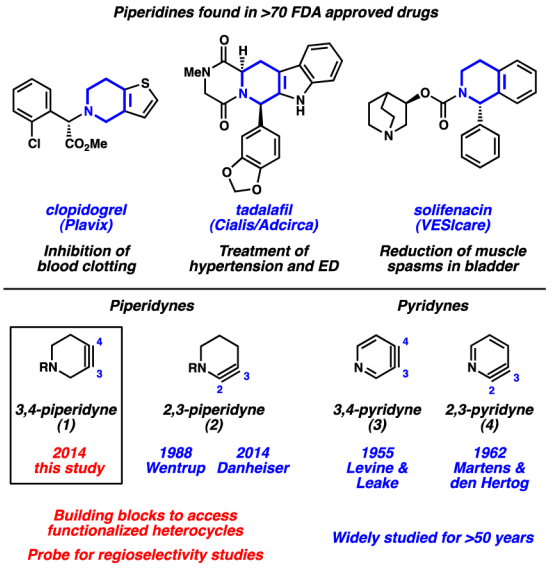


Figure 1. Piperidine-containing blockbuster drugs, piperidynes **1** and **2**, and pyridynes **3** and **4**.

Herein we report: (a) the first generation of a 3,4-piperidyne **1**; (b) the strategic use of **1** to construct a range of functionalized piperidines, many of which possess significant aliphatic character[10] and represent new heterocyclic scaffolds; (c) regioselectivity predictions, observations, and explanations involving the 3,4-piperidyne, which are in accord with the distortion/interaction model;[7a,e,8g] and (d) an explanation for the lack of selectivity observed in trapping experiments of the 3,4-pyridyne (**3**), which has been unresolved for many decades.

We initiated our studies by applying the distortion/interaction model to our targeted piperidyne, Cbz-derivative **1a**,[11] in order to assess the likelihood that it would undergo regioselective trapping in reactions with nucleophiles and cycloaddition partners (Figure 2). In previous studies, we showed that the degree of distortion present in the ground state of arynes and

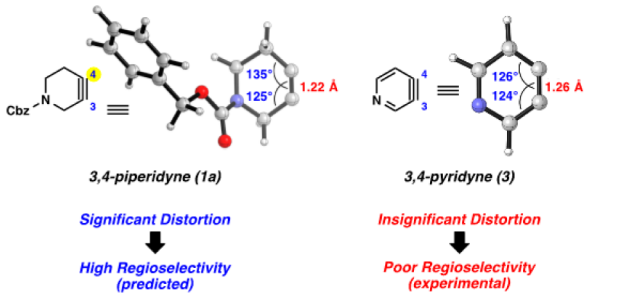


Figure 2. Optimized structures of **1a** and **3** obtained at the B3LYP/6-31G(d) level.

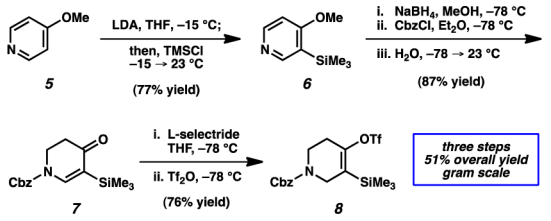
Received: February 12, 2015

DOI: 10.1021/jacs.5b01589
J. Am. Chem. Soc. XXXX, XXX, XXX−XXX

strained alkynes is correlated with the observed regioselectivity because the intermediate is predistorted toward one of two competing transition states.[7a,e,8g,9] Geometry optimization using DFT calculations (B3LYP/6-31G(d)) revealed that **1a** is significantly distorted (ca. 10° difference in internal angles at C4 and C3), such that nucleophilic addition should occur preferentially at the more linear terminus (C4). As a key point of comparison, we also studied 3,4-pyridyne **3**, which is well-known to react with poor regioselectivity,[7a,e,8g,12] as mentioned earlier. In contrast to **1a**, the geometry-optimized structure of **3** shows little unsymmetrical distortion. Given this interesting dichotomy, we envisioned that experimental studies of 3,4-piperidyne **1a** would not only test our regioselectivity predictions but also could ultimately shed light on why 3,4-pyridyne **3** is not significantly distorted and, accordingly, reacts with poor regioselectivity.

The success of our study would rely on the development of an efficient synthesis of a suitable 3,4-piperidyne precursor. After identifying silyl triflate **8** as our target,[11,13] we developed the robust and scalable three-step route shown in Scheme 1.

Scheme 1. Synthesis of Silyl Triflate 8

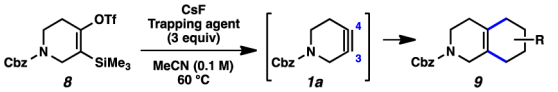


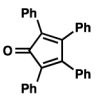
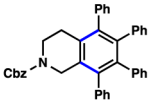
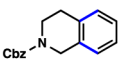
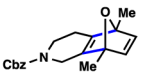
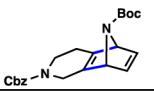
Beginning from commercially available 4-methoxypyridine (**5**), a known procedure was employed to effect ortho silylation to yield silylpyridine **6**.[14] Next, a one-pot procedure involving reductive carbamoylation and hydrolysis[15] provided vinylogous amide **7** in excellent yield. Finally, conjugate reduction followed by trapping of the resultant enolate with Tf_2O[16] provided silyl triflate **8**. The sequence was performed on a gram scale and provided **8** in 51% overall yield from **5**.[17]

To validate that the 3,4-piperidyne could be generated, we performed a series of Diels–Alder trapping experiments to produce a variety of annulated products (Table 1). Specifically, silyl triflate **8** was treated with CsF in the presence of several trapping agents (3 equiv) in acetonitrile at 60 °C. The use of tetracyclone as the trapping agent delivered a tetrahydroisoquinoline product in 76% yield via cycloaddition followed by loss of CO (entry 1). An alternate tetrahydroisoquinoline was accessed upon trapping of the intermediate 3,4-piperidyne with 2-pyrone by way of a Diels–Alder/retro-Diels–Alder sequence with concomitant loss of CO_2 (entry 2). Additionally, cycloadditions with 2,5-dimethylfuran and *N*-Boc-pyrrole provided the corresponding piperidine-fused [2.2.1]-bridged bicyclic products (entries 3 and 4).

Encouraged by our initial success, we carried out trapping experiments of 3,4-piperidyne **1a** with a variety of nucleophiles and unsymmetrical cycloaddition partners (Table 2). In addition to acting as a probe for our regioselectivity predictions, some of the transformations provide access to interesting heterocyclic products. Nucleophilic addition experiments were performed with imidazole and morpholine (entries 1 and 2). In both cases, addition occurred exclusively at C4, consistent with our earlier prediction and differing from the known trends of 3,4-pyridyne reactions. An analogous regiochemical preference was observed in a series of cycloaddition reactions. For example, trapping with

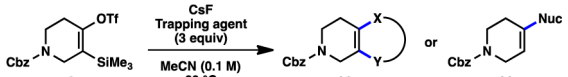
Table 1. Diels–Alder Cycloadditions of 3,4-Piperidyne 1a

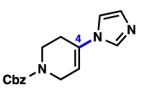
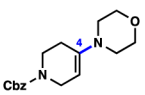
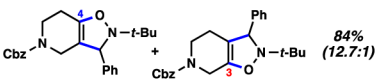
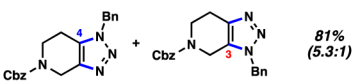
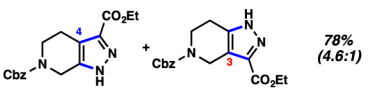
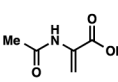
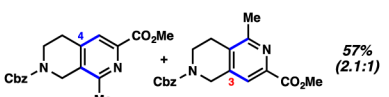
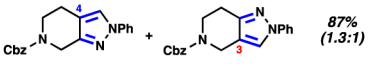


Entry	Trapping agent	Product	Yield[a]
1			76%
2			62%
3			61%
4			66%

[a]Reported yields are averages of two experiments and are based on the amounts of isolated products.

Table 2. Reactions of Silyl Triflate 8 with Nucleophiles and Cycloaddition Partners



Entry	Trapping agent	Product(s)	Yield[a] (ratio)
1			78% (>20:1)
2			99%[b] (>20:1)
3			84% (12.7:1)
4			81% (5.3:1)
5			78% (4.6:1)
6			57% (2.1:1)
7			87% (1.3:1)

[a]Reported yields are averages of two experiments and are based on the amounts of isolated products. [b]The yield was determined using 1,3,5-trimethoxybenzene as an external standard.

a nitrone afforded isoxazoline products in good yield with a significant regiochemical preference of 12.7 to 1 (entry 3). In (3 + 2) cycloadditions using azide and diazo coupling partners, triazole and pyrazole products, respectively, were obtained

DOI: 10.1021/jacs.5b01589
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(entries 4 and 5). Pyridine- and *N*-phenylpyrazole-containing annulated products could be obtained as well, albeit with lower selectivities (entries 6 and 7).[18]

Several salient features regarding this methodology and the products shown in Tables 1 and 2 should be noted. (a) Analogous to known reactions of arynes using silyl triflate precursors, 3,4-piperidyne trapping experiments are operationally trivial to perform and generally do not require the rigorous exclusion of oxygen or moisture. (b) Silyl triflate **8**, which is now being commercialized to enable its widespread use in drug discovery,[17] can be used as a single precursor in order to access a variety of annulated piperidines. This stands in contrast to more conventional strategies, which would involve the development of an independent synthesis of each annulated piperidine desired. (c) Several of the products accessed by our methodology represent new scaffolds, including the unique compounds shown in entries 3 and 4 in Table 1 and entries 3 and 6 in Table 2.[19] (d) Many of the cycloaddition adducts shown in Table 2 are new analogues of known medicinally important scaffolds. For example, compounds related to those in entries 4, 5, and 7 show promise for the treatment of inflammation,[20] diabetes,[21] cancer,[22] hepatitis C,[23] and other illnesses. (e) Finally, with regard to regioselectivity, it should be emphasized that 3,4-piperidyne **1a** uniformly reacts with a preference for initial attack at C4, which is the same trend as seen in reactions of the well-studied 3,4-pyridyne **3**. However, the observed selectivities in the case of **1a** are generally greater than those seen in the trapping of 3,4-pyridynes.[24]

To understand the disparity in the regioselectivities of the reactions of **3** and **1a**, we used DFT calculations to analyze the competing transition states for the nucleophilic addition of morpholine to **3** and compared the results to the corresponding transition states involving **1a** (Figure 3). In the reactions of **3** with morpholine, the difference in the energies for attack at C4 versus C3 (**TS1** and **TS2**, respectively) is negligible. This is consistent with the low regioselectivity seen experimentally.[24,25] As these are very early transition states, the distortion energy (ΔE^{dist}), i.e., the energy required to alter the alkyne geometry toward the transition state, is expected to be small; in fact, we do calculate a slightly greater ΔE^{dist} of the alkyne for **TS2** than **TS1** (ca. 0.2 kcal/mol). In contrast, the addition of morpholine to C4 of 3,4-piperidyne **1a** (**TS3**) is predicted to be favored over attack at C3 (**TS4**) by roughly 1.7 kcal/mol. Notably, the disparity in ΔE^{dist} accounts for most of the energetic difference and the resulting high regioselectivity observed experimentally (see Table 2, entry 2). These results validate that the distortion/interaction model correctly predicts and explains the regioselectivities in reactions of both **3** and **1a**.

As noted earlier, the lack of regioselectivity seen in reactions of 3,4-pyridynes has been a long-standing problem. Thus, we sought to probe one remaining critical question: why is the 3,4-piperidyne significantly distorted while the 3,4-pyridyne is not? The explanation is summarized in Figure 4. The distortion of 3,4-piperidyne **1a** is caused by the electronegativity of the N heteroatom, which deforms the triple bond as a result of Bent's rule.[26] The internal bond angle at C3 is decreased, mixing in p character at C3 and releasing electron density toward the electronegative N atom. Although the analogous effect is also present in 3,4-pyridyne **3**, it is offset by the in-plane overlap of the nitrogen lone pair with the π and π^* orbitals at C3, which causes C3 to move toward the N atom (for further discussion of these competing effects, see the Supporting Information). Such an effect is not seen in **1a**, as the nitrogen lone pair is orthogonal to the π and π^* orbitals of the alkyne.

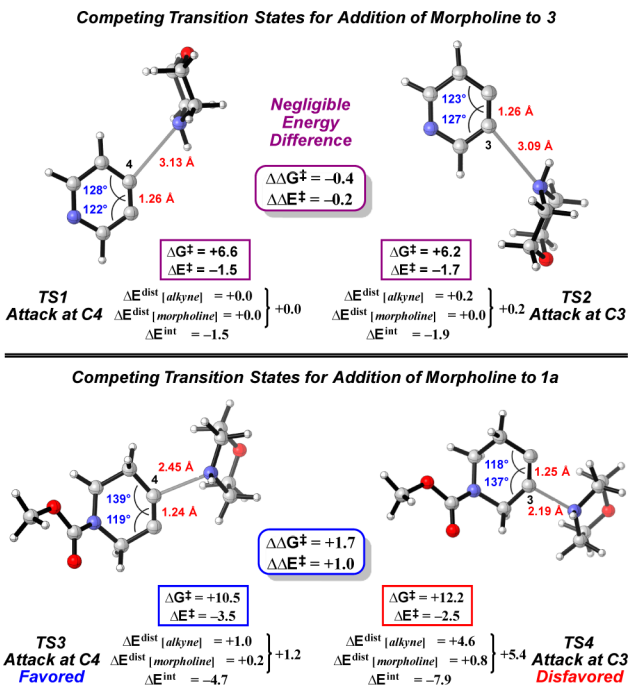

Figure 3. Optimized transition states for nucleophilic addition of morpholine to **3** and **1a** at the B3LYP/6-31G(d) level. Single-point energies were calculated at the B3LYP-D3/6-311+G(d,p) level with the CPCM solvent model for MeCN. Energies are provided in kcal mol^{-1}.

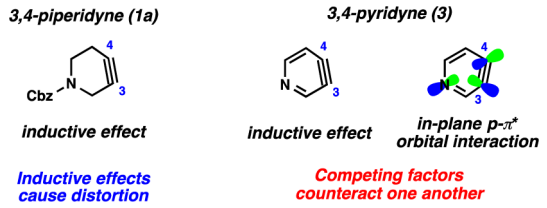

Figure 4. Explanation of the differing distortion seen in **1a** and **3**.

In summary, we have synthesized the first 3,4-piperidyne, **1a**, and demonstrated that this reactive intermediate can be utilized in a variety of cycloadditions to form annulated piperidine scaffolds. The regioselectivity trends observed in reactions of **1a** with nucleophiles and unsymmetrical cycloaddition partners are predicted and rationalized by the distortion/interaction model. Moreover, we have explained the inductive effect that causes the distortion seen in **1a** in addition to the competing inductive effects and orbital interactions that result in the lack of regioselectivity observed in reactions of the well-studied 3,4-pyridyne (**3**). Our findings not only provide a new platform to access medicinally privileged piperidine scaffolds, but also lay the foundation for further studies geared toward strategically harnessing strained heterocyclic alkynes as useful synthetic building blocks.

■ ASSOCIATED CONTENT

Supporting Information

Detailed experimental and compound characterization data. This material is available free of charge via the Internet at http://pubs.acs.org.

DOI: 10.1021/jacs.5b01589
J. Am. Chem. Soc. XXXX, XXX, XXX−XXX

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Notes

The authors declare no competing financial interest.

ACKNOWLEDGMENTS

The authors are grateful to the NIH NIGMS (R01 GM090007 to N.K.G.), the National Science Foundation (CHE-1361104 to K.N.H.), Bristol-Myers Squibb, DuPont, the Alfred P. Sloan Foundation, the S. T. Li Foundation, the Dreyfus Foundation, the UC Cancer Research Coordinating Committee, and the UCLA Cota Robles Fellowship Program (J.M.M.) for financial support. This work used the Extreme Science and Engineering Discovery Environment (XSEDE), which is supported by the National Science Foundation (OCI-1053575) along with the UCLA Institute of Digital Research and Education (IDRE). These studies were supported by shared instrumentation grants from the NSF (CHE-1048804) and the National Center for Research Resources (S10RR025631).

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(9) For a recent study of cyclohexynes and cyclopentyne, see: Medina, J. M.; McMahon, T. C.; Jiménez-Osés, G.; Houk, K. N.; Garg, N. K. *J. Am. Chem. Soc.* **2014**, *136*, 14706.

(10) The ability to access heterocyclic scaffolds with significant aliphatic character is an important direction in modern drug discovery. See: (a) Lovering, F.; Bikker, J.; Humblet, C. *J. Med. Chem.* **2009**, *52*, 6752. (b) Ritchie, T. J.; Macdonald, S. J. F. *Drug Discovery Today* **2009**, *14*, 1011.

(11) The carboxybenzyl (Cbz) protecting group was chosen because of its pronounced stability and its ability to be selectively cleaved.

(12) For recent examples of 3,4-pyridyne regioselectivities, see: (a) Enamorado, M. F.; Ondachi, P. W.; Comins, D. L. *Org. Lett.* **2010**, *12*, 4513. (b) Saito, N.; Nakamura, K.-i.; Shibano, S.; Ide, S.; Minami, M.; Sato, Y. *Org. Lett.* **2013**, *15*, 386. (c) Saito, N.; Nakamura, K.-i.; Sato, Y. *Heterocycles* **2014**, *88*, 929.

(13) Given the widespread use of silyl triflates in aryne and cycloalkyne trapping experiments (using mild fluoride-based conditions), we deemed silyl triflate to be **8** an ideal target.

(14) Comins, D. L.; Joseph, S. P.; Goehring, R. R. *J. Am. Chem. Soc.* **1994**, *116*, 4719.

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(17) Aldrich Chemical Co, Inc. is currently commercializing silyl triflate **8**, which will be available by mid 2015.

(18) For entry 6, substantial mass was lost to nonproductive reaction pathways, which may render the regioselectivity data unreliable. In the case of entry 7, the lack of regioselectivity can be attributed to the sydnone trappings occurring through concerted, highly synchronous transition states with low activation barriers. Larock and Shi have reported similarly modest regioselectivities using 3-methoxybenzyne with the sydnone trapping agent. See: Fang, Y.; Wu, C.; Larock, R. C.; Shi, F. *J. Org. Chem.* **2011**, *76*, 8840.

(19) Structural similarity searches were performed using SciFinder Scholar. Other scaffolds, including the minor adduct from the diazo ester cycloaddition (Table 2, entry 5) and the major product from the sydnone cycloaddition (Table 2, entry 7) are also difficult to access.

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(24) Comparative regioselectivity data for the reactions of **3** and **1a** are summarized below (C4 attack favored in all cases). For piperidyne regioselectivity data, see Table 2 and the Supporting Information. For pyridyne regioselectivity data, see ref 8a and: Goetz, A. E.; Garg, N. K. Unpublished results. For additional pyridyne azide cycloaddition regioselectivity data, see ref 12c .

Reactive Species	Regioselectivity with Morpholine	Regioselectivity with N-Me-Aniline	Regioselectivity with Nitrone	Regioselectivity with Azide
3	1.3 : 1	1.9 : 1	1.9 : 1	1.7 : 1
1a	>20 : 1	>20 : 1	12.7 : 1	5.3 : 1

(25) Considering the standard error associated with computations and that the transition states are very early with low barriers, we consider the computational and experimental findings to be in reasonable accord.

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DOI: 10.1021/jacs.5b01589
J. Am. Chem. Soc. XXXX, XXX, XXX−XXX