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Synthesis of Pyrrole-Fused *C,N*-Cyclic Azomethine Imines and Pyrazolopyrrolopyrazines: Analysis of Their Aromaticity Using Nucleus-Independent Chemical Shifts Values

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Supporting Information

ABSTRACT: The AgOTf-catalyzed reaction of C-2 substituted pyrrole hydrazones having an *N*-propargyl group was studied. The selective 6-*endo*-*dig* mode of cyclization was observed, giving rise to the formation of pyrrole-fused *C,N*-cyclic azomethine imine derivatives. The reaction of one azomethine imine derivative with various dipolarophiles resulted in the formation of cycloadducts having a pyrazolopyrrolopyrazine skeleton. The aromaticity of *C,N*-cyclic azomethine imines as well as that of pyrazolopyrrolopyrazines was determined by calculating of nucleus-independent chemical shifts values.

Most of the azomethine imines are formed as intermediates, and they can be trapped with electron-deficient dipolarophiles or simple alkenes to form five-membered heterocycles.[1] There are two types of azomethine imines: acyclic imines and cyclic azomethine imines. The latter can be split into three classes: *C,N′*-cyclic **1**,[2] *N,N′*-cyclic **2**[3] with two atoms incorporated into a ring, and *C,N,N′*-cyclic **3**[4] with three atoms embedded in a ring (Figure 1).

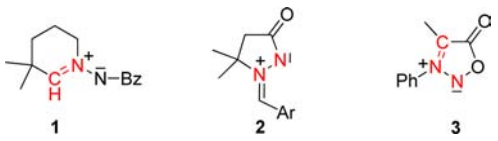

Figure 1. Structures of different classes of cyclic azomethine imines.

Tamura et al.[5] reported the synthesis of a benzene-fused *C,N′*-cyclic azomethine imine as a metastable compound and, more recently, Maruoka et al.[2,6] exploited the applicability of these intermediates to the synthesis of various heterocycles with excellent enantioselectivity.

There are two general pathways to obtain *C,N′*-cyclic azomethine imines. Azomethine imines can be prepared upon heating appropriate alkynylhydrazide precursors[7] or by the cyclization of *N*-(2-alkynylbenzylidene)-hydrazide with I_2 or Br_2.[8] The latter is a metal-catalyzed intramolecular cyclization reaction between alkyne and *N′*-acyl hydrazones. Wu et al. used a silver triflate-catalyzed reaction of 2-alkynyl-benzaldehyde and tosylhydrazide to generate azomethine imines as the intermediates, which were successfully trapped.[9]

Among the various transition metals, silver-catalyzed tandem sequences have attracted considerable attention due to their ability to activate various π-systems under very mild conditions and at low catalyst loading.[10] The trapping of *C,N′*-cyclic azomethine imines with different reagents gives access to pharmaceutically attractive compounds.[11]

Furthermore, enantiocatalyzed 1,3-dipolar cycloadditions of azomethine imines to various dipolarophiles were applied to the synthesis of various new heterocycles with biological activities.[12]

C,N′-Cyclic azomethine imines are generally found as a part of pyridine (**4**)[13] or pyridine analogues such as quinoline (**5**) and isoquinoline (**6**) (Figure 2).[14] The limit of these substrates may

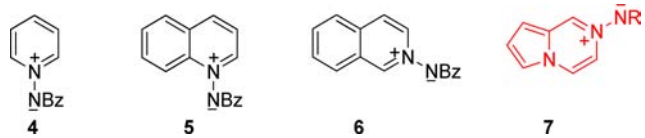

Figure 2. Structures of common *C,N′*-cyclic azomethine imines.

block the extension of scope of many important heterocyclic molecules that might be vital in pharmaceutical fields. Accordingly, we have developed a synthetic way to obtain pyrrole-fused *C,N′*-cyclic azomethine imine derivatives **7** via a silver-catalyzed reaction. Herein, we describe their synthesis and trapping with dipolarophiles and analyze their aromaticity using nucleus-independent chemical shifts (NICS) values.

The starting materials **9** and **10** were prepared according to the literature. Pyrrole aldehyde **8** was synthesized by application of the Vilsmeier reaction.[15] Treatment of aldehyde **8** with propargyl

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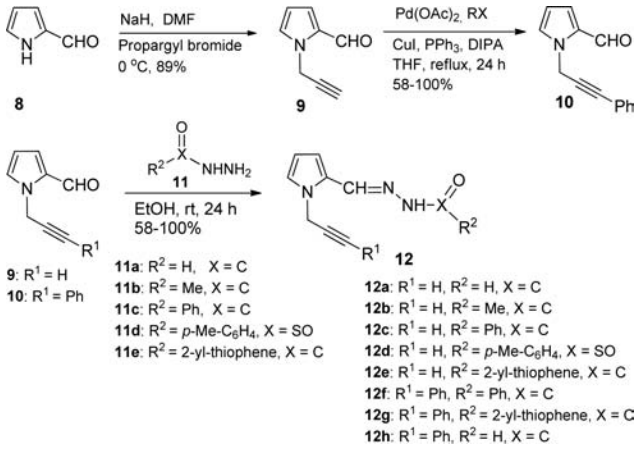
bromide followed by Sonogashira coupling afforded the alkyne derivatives **9**[16] and **10**[17] (Scheme 1). *N*-Propargylpyrrole-2-*N*′-

Scheme 1. Synthesis of *N*-Propargylpyrrole-2-hydrazones 12a−h



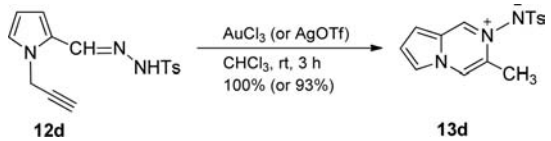
acyl and tosyl hydrazones **12a−h** were synthesized by the reaction of *N*-propargyl-2-formylpyrrole with various hydrazines substituted by tosyl or acyl groups in excellent yields (Scheme 1).

The ^{1}H NMR spectra of **12b** and **12e** revealed the formation of (*E*)- and (*Z*)-hydrazone isomers. The signals of (*E*)- and (*Z*)-hydrazones differ significantly, up to 0.2 ppm. An isomeric (*E*)- and (*Z*)-hydrazones mixture was used for further reactions.

We next examined the feasibility of the intended synthetic approach to the target pyrrole-fused *C*,*N*′-cyclic azomethine imine derivatives **7**. For this purpose, the hydrazone derivatives **12a−h** were submitted to a cyclization reaction. We selected tosyl hydrazide **12d** as a model substrate for the initial experiments.

For cyclization, gold and silver salts and complexes have emerged the most powerful catalysts for electrophilic activation followed by the reaction with nucleophiles.[18] The reaction of **12d** with $AuCl_3$ in chloroform at room temperature gave rise to the formation of cyclization product **13d** in quantitative yield (Scheme 2). The spectral data of **13d** were in complete agreement with the proposed structure. Finally, the structure of **13d** was further confirmed by single-crystal X-ray analysis (Figure 3).

Scheme 2. Synthesis of Pyrrole-Fused *C*,*N*′-Cyclic Azomethine Imine Derivative 13d



Encouragingly, when we treated model substrate **12d** with silver trifluoromethanesulfonate ($AgOSO_2CF_3$) under the same reaction conditions the cyclization product **13d** was again formed in 93% yield.

To extend the scope of the cyclization reaction and to see the effect of the acyl substituents and of groups attached to the terminal alkyne, such as the phenyl group, hydrazone derivatives were reacted first with $AuCl_3$ as the catalyst. We observed that substitution at the terminal carbon atom of a propargyl group

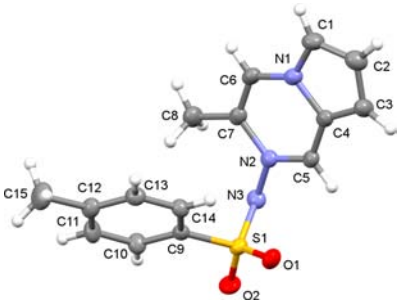


Figure 3. Single-crystal X-ray structure of **13d**.

with a phenyl group did not give the corresponding cyclization products as the sole compounds. The triple bond was partly converted to ketone. It is well-known that gold-activated water intermediates can easily be added to conjugated alkynes.[19] Therefore, all hydrazone derivatives **12a−h** were submitted to AgOTf-catalyzed cyclization reactions. The first outcome was that no substituent effect was observed when the group attached to the triple bond (hydrogen or phenyl) was changed. The reactions also worked well when the acyl group on the nitrogen atom was changed to formyl, benzoyl, thienoyl, and sulfonyl (Figure 4). All compounds **13a−h** were properly characterized by spectral data.

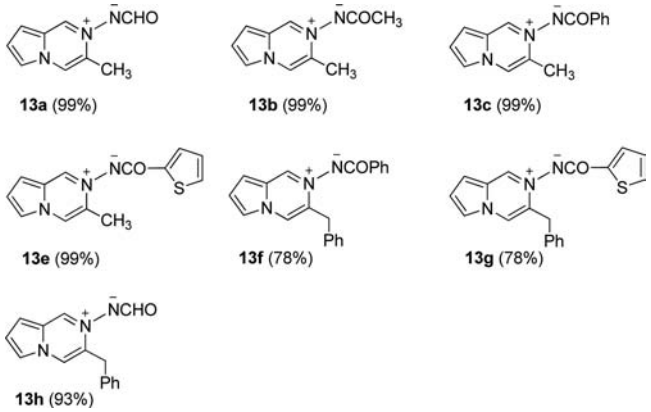


Figure 4. Pyrrole-fused *C*,*N*′-cyclic azomethine imine derivatives **13a−c**,**e−h**.

The proposed catalytic cycle was initiated by the activation of the triple bond by $AuCl_3$ to form the intermediate **B**, which undergoes a nucleophilic attack by the nitrogen atom of hydrazine to give the intermediate **C**, which led to the formation of azomethine imine **E** through **D** (Scheme 3).

1,3-Dipolar cycloaddition is one of the most ideal synthetic methods for the construction of five-membered heterocycles. We report herein the exploitation of unexplored *C*,*N*-cyclic azomethine imine **15d** in 1,3-dipolar cycloaddition, giving access to pyrazolopyrrolopyrazines.[20] Gratifyingly, the reaction of acrylonitrile with azomethine imine derivative **13d** proceeded smoothly at the reflux temperature of toluene to give the cycloadduct **14** in 44% yield (Scheme 4).

With this promising result in hand, we investigated the generality of this 1,3-dipolar cycloaddition reaction with acrylaldehyde, methyl acrylate, and dimethylacetylene dicarboxylate, furnishing the cycloadducts **15−17** in 37−50% yields and regioselectivities (Figure 5).

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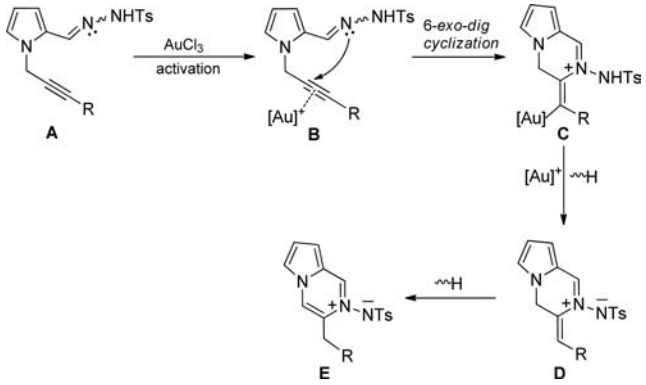
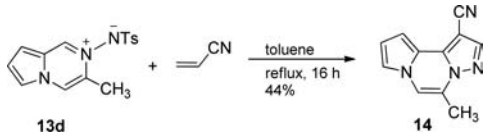
Scheme 3. Proposed Reaction Mechanism for the Intramolecular Gold-Catalyzed Cyclization of Hydrazones 12



Scheme 4. Construction of the Pyrazolopyrrolopyrazine Skeleton 14



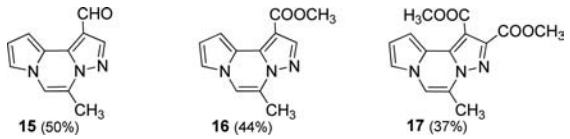
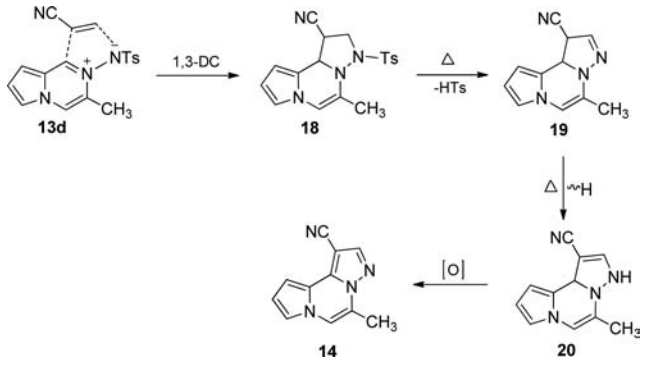


Figure 5. Pyrazolopyrrolopyrazine derivatives **15**–**17**.

We propose the following mechanism for the formation of **14**. The zwitterion **13d** first undergoes a [3 + 2] cycloaddition reaction with the dipolarophiles to give the nonaromatic pyrazolidine **18** (Scheme 5). We envisage that this intermediate

Scheme 5. Proposed Mechanism for the Formation of 14



18 is subjected to elimination of *p*-toluenesulfinic acid under the thermal conditions followed by an H-shift to give the dihydropyrazole derivative **20**. Air oxidation results in the formation of the final product **14**.[21] The exact location of the aldehyde group in **15** was determined from the HMBC spectrum, which showed a strong correlation between the aldehyde proton resonating at 10.1 ppm with two carbon atoms: imine carbon atom and the quaternary carbon atom of the pyrazole ring resonating at 144.3 and 116.2 ppm, respectively. We assume that the formation of a fully conjugated system is the driving force of this oxidation reaction.

To test the aromaticity[22] in some selected *C,N*-cyclic azomethine imines **13a**–**f** as well as in pyrazolopyrrolopyrazines **14**–**17** we calculated the NICS[23] values. There are many criteria for characterizing aromaticity. NICS has become the most widely used aromaticity probe due to its simplicity and efficiency. Negative NICS values denote aromaticity and positive NICS values antiaromaticity. Negative NICS values are defined as the negative value of absolute shielding observed at a ring center (NICS(0)) or at some other interesting points of the system, usually 1 Å above the ring center (NICS(1)). Benzene has a NICS(0) value of −9.7, whereas the antiaromatic cyclobutadiene has a value of 22.7.

The NICS(0) values (−16.3 to −18.2) of *C,N*-methines **13a,c,d,f** for pyrrole rings resemble that of pyrrole (−16.0) (Figure 6). On the other hand, the NICS(0) values of the

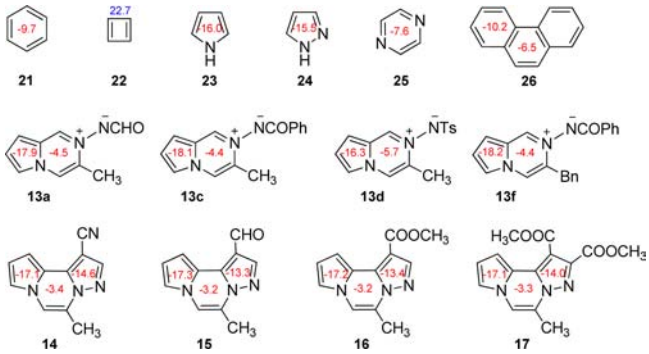


Figure 6. NICS(0) values for selected compounds. The NICS(0) values for compounds **21**, **22**, and **26** were taken from ref 23.

pyrazine rings are reduced showing that the pyrrole rings are more aromatic than the pyrazine rings. Upon annulation of pyrazole rings, the aromaticity in the pyrrole rings of **14**–**17** is not affected so much. However, the aromaticity in the pyrazine rings is further reduced. These values may be compared with the NICS(0) value of **26**. Pyrazole rings in **14**–**17** show a more aromatic character. This may be the driving force of the intermediate **20** to easily undergo an oxidation reaction upon exposure to air. Furthermore, we observed that the substituents do not have a remarkable influence on NICS(0) values.

In conclusion, we have revealed an applicable method to obtain excess pyrrole-fused *C,N*-cyclic azomethine imine derivatives **13a**–**h** starting from *N*-propargyl derivatives substituted with hydrazone functionality at the C-2 position of the pyrrole ring. The AgOTf-catalyzed cyclization reaction of these starting materials provided pyrrole-fused *C,N′*-cyclic azomethine imine derivatives **13a**–**h**. Lastly, the reaction of azomethine imine derivative **13d** with various dipolarophiles with electron-withdrawing substituents gave the cycloadducts **14**–**17** having a pyrazolopyrrolopyrazine skeleton in high yields.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.5b03434.

Experimental conditions, spectroscopic data (1D and 2D NMR spectra) of the products, X-ray crystal structure of **13d**, and Cartesian coordinates for the optimized structures (PDF)

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Notes

The authors declare no competing financial interest.

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