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A missing member of conjugated N-heterocycles: realizing pyrido[1,2-α]azepine by reacting ruthenium alkenylcarbene complex with alkyne†

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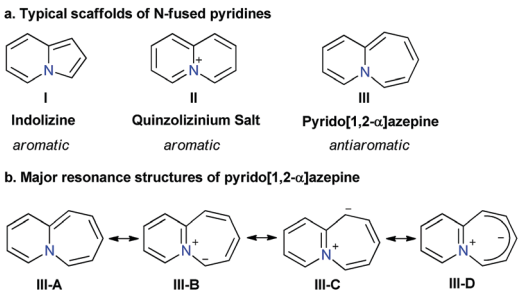
Despite the excellent chemical properties of N-heterocycles, pyrido-[1,2-α]azepine remains elusive due to its potential antiaromaticity and lability. Herein, we demonstrate the synthesis and characterization of the first bicyclic pyrido[1,2-α]azepine that leverages the coordination to the ruthenium center to promote the stability of N-bridged bicycle.

N-Heterocyclic compounds are widely found in naturally occurring compounds and have a broad range of applications in pharmaceutical research and materials science.[1] Among these compounds, N-fused pyridines have been regarded as a particular family of heterobicycles with a bridgehead nitrogen atom.[2] As shown in Scheme 1a, indolizines (**I**) and quinolizinium salts (**II**) are the most typical scaffolds of N-fused pyridines. They are particularly significant aromatic backbones in bioactive compounds and organic functional materials,[3] and the synthetic investigations of these compounds have earned fruitful achievements.[4] However, the intimate analogue of **I** and **II**, *viz.*, pyrido[1,2-α]azepines **III** (pyridine fused with a conjugated seven-membered ring) remains elusive and thus represents a missing member in this well-explored field. It is considered that inherent antiaromaticity and unstability are responsible for its absence. Although it is expected that some stabilization could be achieved by virtue of the carbon betaine resonance structures (**III-B** to **III-D**, Scheme 1b), the synthetic attempt to trap this bicyclic ring system was unsuccessful.[5] The lack of pyrido[1,2-α]azepine **III** has greatly restrained the understanding and application of this ring system despite their potential biosynthetic and medicinal interest.

Seeking unprecedented and exciting N-heterocyclic scaffolds is one of the most important goals in chemistry and this momentum has never stopped.[6] In general, aligning labile organic species with transition metal centers is an effective strategy to stabilize highly labile frameworks. Various unstable species demonstrate enhanced stability with this strategy, which has been studied extensively.[7] Thus, it appears to be feasible to achieve the pyrido[1,2-α]azepine in the coordination sphere of a transition metal. Herein, we report the synthesis and full characterization of a persistent pyrido[1,2-α]azepine complex by the [2+2] cycloaddition reaction of pyridyl-coordinated ruthenium–alkenylcarbene complex with alkyne. The reaction outcomes are significantly dominated by the effect of substituents on alkynes and density functional theory (DFT) calculations are performed to further elucidate the experimental findings.



Scheme 1 Background.

As shown in Scheme 2, treatment of ruthenium–carbene **1** with cyclopropylethyne at room temperature led to the formation of ruthenium complex **2**. Complex **2** was isolated as an orange solid by recrystallization with a yield of 65%. The structure of **2** was confirmed by single-crystal X-ray diffraction (Fig. 1), revealing that the N-fused bicyclic backbone adopts a cyclopropyl-substituted pyridoazepine conformation, in which the seven-membered N-heterocycle was formed from the two-atom contribution of the alkyne. Ru(II) exhibits a typical three-legged piano-stool structure featuring five carbon atoms of the pyrido[1,2-α]azepine ring connected to the metal center as an η^5-coordinated ligand. The η^5-coordinated unit (C1, C2, C3, C4, and C5) in **2** is nearly

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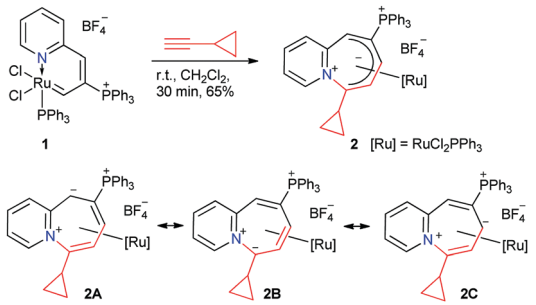


Scheme 2 Synthesis and major resonance structures of pyrido[1,2-α]-azepine–ruthenium complex **2**.

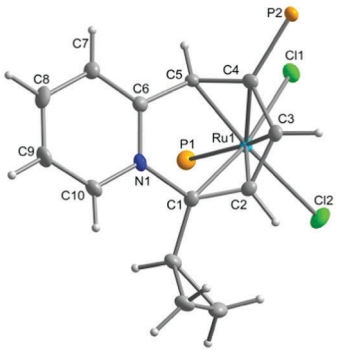


Fig. 1 Single-crystal X-ray structure for cationic complex **2** with thermal ellipsoids drawn at the 50% probability level. The phenyl groups in the triphenylphosphine (PPh_3) moieties were omitted for clarity.

coplanar as reflected by the small mean deviation from the least-squares plane (0.0273 Å). The pyridine unit, C1, and C5 are also coplanar with a small mean deviation from the least-squares plane of 0.0294 Å. The distorted configuration of the bicyclic pyrido[1,2-α]azepine system is indicated by the dihedral angle of the two planes (127°). The C–C bond lengths of the seven-membered ring (C1–C2, 1.422(4) Å; C2–C3, 1.407(4) Å; C3–C4, 1.415(4) Å; C4–C5, 1.457(4) Å; C5–C6 1.467(4) Å) are intermediate between those of typical C–C single and double bonds despite the slightly longer lengths of C4–C5 and C5–C6. The X-ray diffraction data indicate that the structure of **2** can be rationalized by three resonance structures shown in Scheme 2 with **2A** as the major contributor. The chemical shift of the proton at C5 is located at 2.60 ppm in the ^{1}H NMR spectrum, which agrees with the anticipated structure **2A**. Compared to C^3*H* (6.67 ppm) and C^2*H* (4.80 ppm), the considerable high-field shift of C^5*H* should be attributed to the shielding effect of the adjacent phenyl group. Our strategy of generating unusual ligand systems in the coordination sphere of transition metals has enabled us to access the previously elusive pyrido[1,2-α]azepine scaffold and thus, we present the first successful chemical synthesis of the bicyclic pyridoazepine system.

The aromaticity of the typical scaffolds of N-fused pyridines, as shown in Scheme 1a, were theoretically studied with the aid of DFT calculations (Fig. 2, for detailed analysis see ESI,† Table S1 and Fig. S1). Both the nucleus-independent chemical shift (NICS)[8] calculation and the anisotropy of induced current

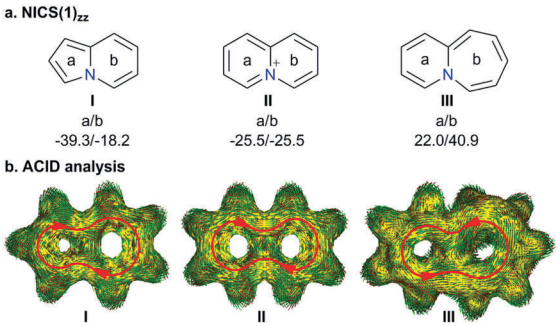
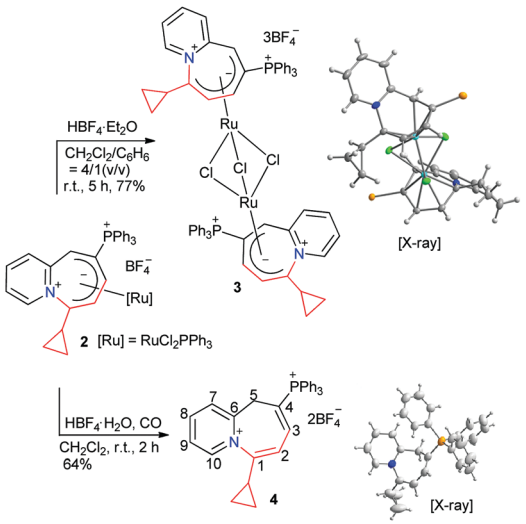
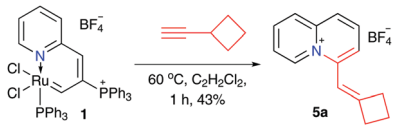


Fig. 2 (a) NICS(1)$_{zz}$ (ppm) evaluations of **I**, **II**, and **III**. (b) ACID plots of **I**, **II**, and **III** with an isosurface value of 0.025. The magnetic field vector is orthogonal to the ring plane and points upward (aromatic species exhibit clockwise diatropic circulations, antiaromatic species exhibit counterclockwise paratropic circulations).

density (ACID)[9] analysis clearly demonstrated the aromaticity of **I**/**II** and antiaromaticity of **III**. These are consistent with previous inference reported in the literature, stating that the isolation of bicyclic pyrido[1,2-α]azepine is unavailable due to its antiaromatic and labile nature.[5] Attempts to release the pyridoazepine unit from the metal center had failed although we tested a number of strong ligands. It should be note that the combination of pyrido[1,2-α]azepine with the ruthenium moiety in **2** is robust. The reaction of **2** and a tetrafluoroboric acid diethyl ether complex ($HBF_4{\cdot}Et_2O$) at room temperature resulted in the formation of the dimer complex **3** containing two ruthenium units connected by three chloro bridges (Scheme 3). Interestingly, the addition of an HBF_4 water complex ($HBF_4{\cdot}H_2O$) to **2** under carbon monoxide (CO) atmosphere led to the dissociation of the pyrido[1,2-α]azepine unit from the metal center and gave the protonation product **4** with a yield of 64%. As shown in Scheme 3, X-ray diffraction confirmed that the isolated N-fused bicycle corresponded to pyrido[1,2-α]azepinium. The CH_2 group of the seven-membered ring in **4** appeared as two triplet signals centered at 4.06 and 3.92 ppm with $^3J_{P-H}$ and $^2J_{H-H}$ couplings of 11.0 Hz and 11.0 Hz, respectively.



Scheme 3 Reactions of **2** with fluoboric acid.



Scheme 4 Reaction of **1** with cyclobutylethyne.

Under the similar reaction conditions for the formation of complex **2**, a number of substituted alkynes were examined to probe whether other pyridoazepine products would be obtained. However, new N-heterocyclic species were detected when other alkynes with cycloalkyl substituents were treated with ruthenium–alkenylcarbene **1**. As shown in Scheme 4, treatment of ruthenium–carbene **1** with cyclobutylethyne, at 60 °C led to the formation of quinolizinium salt **5a**. Other alkynes with cycloalkyl or alkyl substituents such as cyclopentylethyne, cyclohexylethyne, 3-methylbut-1-yne or hex-1-yne also tolerated this reaction, leading to the corresponding quinolizinium salts **5b–5e** (Scheme S1, ESI†).

We propose a plausible mechanism for the formation of **2** and suggest a possible reason for the unique performance of cyclopropylethyne with the aid of DFT calculations. As shown in Fig. 3, initial coordination of the cyclopropylethyne to the ruthenium center forms intermediate **A**. Then, **A** undergoes [2+2] cycloaddition and cycloreversion to generate intermediate **B**. Transformations involving similar processes have been extensively studied in literature,[10] particularly in the synthesis of diverse cyclic structures. The direct reductive elimination of **B** would lead to the formation of a seven-membered azepine unit (path a). Coordination of PPh_3 could furnish the desired pyrido[1,2-α]azepine–ruthenium complex **2**. The key step for the formation of quinolizinium salt **2′**, *i.e.*, from intermediate **B** to **C′** *via* 1,2-H shift is depicted in Fig. 3 as path b (the detailed mechansim is shown in Scheme S2, ESI†). DFT calculations were performed to understand the reductive elimination and 1,2-H shift steps, *i.e.*, paths a and b for the reactions with cyclopropylethyne and cyclobutylethyne. Fig. 4 shows that the formation of pyridoazepine species **C** through reductive elimination (path a) in the reaction with cyclopropylethyne is kinetically and thermodynamically more favourable than path b. However, the energy profile (Fig. S4, ESI†) calculated for cyclobutylethyne indicates that the 1,2-H shift path for the formation of quinolizinium salt **5a** was kinetically less favourable than the reductive elimination path,

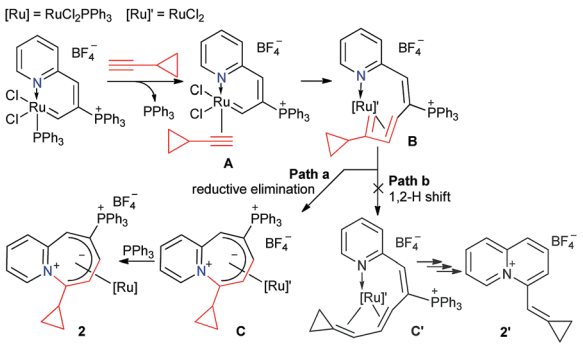


Fig. 3 The plausible mechanisms for the formation of the pyrido[1,2-α]azepine–ruthenium complex **2**.

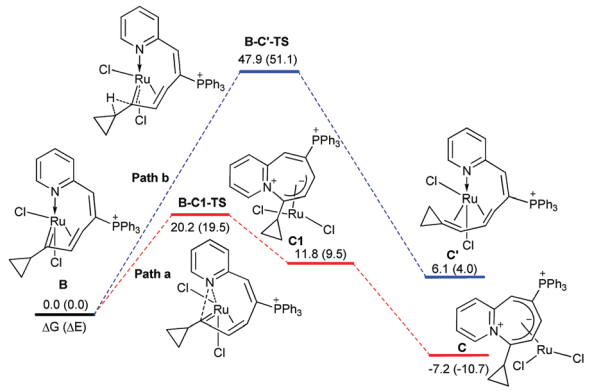


Fig. 4 Energy profiles of the key intermediates with a cyclopropyl substituent in the elimination or 1,2-H shift reaction pathway (labelled in red and blue, respectively). The relative Gibbs free energies and electronic energies (in parentheses) are given in kcal mol^{-1}.

but it was thermodynamically more favourable. Consistent with the calculations, only the reaction with cyclopropylethyne afforded the pyrido[1,2-α]azepine–ruthenium complex. We reasoned that the ring strain of the cyclopropyl substituent impedes the formation of exocyclic double bond, corresponding to the structure **C′** with high relative energy as well as high energy barrier (47.9 kcal mol^{-1}). The strain energy difference of the small rings with exocyclic double bonds has been demonstrated in literature.[11] The outcome of the reaction is consistent with the previous calculations on ring strain of methylenecyclopropane (41 kcal mol^{-1}), which is clearly greater than that of methylenecyclobutane (29 kcal mol^{-1}).

We also tested alkynes without α-proton, such as *tert*-butylacetylene and phenylacetylene. However, *tert*-butylacetylene did not react with ruthenium–alkenylcarbene complex **1**, while the reaction of **1** with phenylacetylene produced a mixture of unidentified species. In our previous study, we showed that acetylenic ketone or alkynoates can react with **1**, leading to the formation of indolizines **I**.[12] Together with the DFT calculations discussed above, these experimental results suggest that the formation of pyridoazepine skeleton should be attributed to a combination of steric and electronic effect of the substituents on the C–C triple bonds.

In summary, the synthesis and X-ray crystallography characterization of the first bicyclic pyrido[1,2-α]azepine ring system was achieved through a [2+2] cycloaddition reaction of ruthenium alkenylcarbene complex with alkyne. Our experimental and computational studies demonstrated that the steric and electronic effect of the substituents on the alkynes are very important for the formation of the fused N-heterocycles. The realization of pyrido[1,2-α]azepine scaffold triumphantly replenishes a long vacancy of N-bridged heterocycle library. We believe that these findings will promote further theoretical and experimental investigations of pyrido[1,2-α]-azepine systems and facilitate the design of N-bridged heterocycle toward biological and pharmaceutical applications.

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Conflicts of interest

The authors declare no competing financial interests.

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