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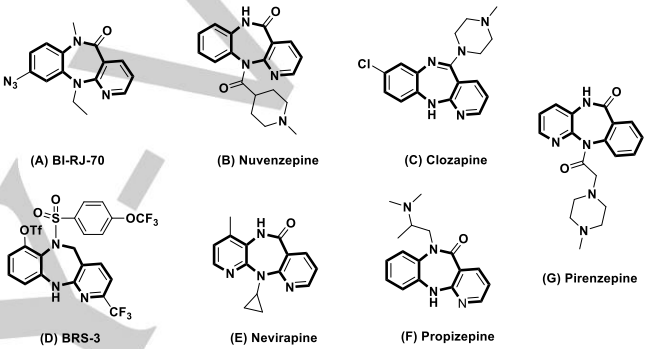
Synthesis of Benzodiazepines *via* Ring Opening/Ring Closure of Benzimidazole Salts

Sheng Tao,[a] Qingqing Bu,[a] Qianqian Shi,[b] Donghui Wei,*[b] Bin Dai,*[a] and Ning Liu*[a]

Abstract: Pyrido-benzodiazepine derivatives are undoubtedly one of the most important structural motifs in the marketed drugs and the drug candidates. Commonly synthetic methods for construction of the benzodiazepine ring derivatives are based on the condensation reactions of two highly functionalized synthons. The development of synthesis for these compounds, however, is hampered by the regioselectivity and atom economy. In this work, a one-step synthesis of pyrido-benzodiazepine backbones and its analogues is achieved through continuous ring-opening hydrolysis of benzimidazole salts and intramolecular C−H bond activation. The reaction mechanism is explored by the control experiments and density functional theory calculations (DFT) method.

Introduction

Pyrido-benzodiazepine derivatives are ubiquitous structural core of many synthesized molecules with widespread applications in clinical medicines.[1] In particular, benzo- and pyridino-diazepine compounds are important heterocyclic derivatives used extensively in pharmaceutical application.[2] For example, various benzo- and pyrido-benzodiazepine derivatives find important uses in several marketed pharmaceuticals, such as BI-RJ-70,[3] Nuvenzepine,[4] Clozapine,[5] BRS-3,[6] Nevirapine,[7] Propizepine,[8] and Pirenzepine[9] (Scheme 1). Consequently, the development of methods for the synthesis of pyrido-benzodiazepine compounds is important in medicinal chemistry and represents a worthwhile goal for organic synthesis.[10]
Commonly synthetic methods for construction of pyrido-benzodiazepine derivatives are based on the condensation reactions of two highly functionalized synthons (Scheme 2, pathways 1 and 2). A most frequently used approach is the condensation of substituted *ortho*-phenyldiamine with 2-chloronicotinic acid to achieve pyrido-benzodiazepine compounds.[6, 9b, 11] However, this method led to a regioisomeric mixture of products due to poor regioselectivity of two NH_2 of benzene ring is difficult to control (Scheme 2, pathway 1).[6a, 12] In addition, the aforementioned resulting products also suffered from poor site selectivity at two NH with pyrido-benzodiazepine for further being *N*-functionalization (Scheme 2, pathway 1). To overcome above disadvantage in pathway 1 caused by *ortho*-phenyldiamine, various coupling partners, such as *ortho*-nitroaniline,[12] 2-chloropyridin-3-amine,[13] 2-aminobenzoic acid,[14] methyl 2-aminobenzoate,[15] 2-bromobenzamide,[16] as well as three-components system,[17] have been used to displace the *ortho*-phenyldiamine for the synthesis of pyrido-benzodiazepine compounds, with a focus on achieving high selectivity (Scheme 2, pathway 2).



Scheme 1. Scaffolds of pyrido-benzodiazepine compounds.

Despite replacing of starting materials could achieve a significant improvement in selectivity, the wide, atom-economic and sustainable application of current developed method is hindered by the need for the multistep sequences, and/or the employment of *N*-protecting groups. Although synthetic strategies for synthesis of benzodiazepine ring derivatives have been widely explored, it is highly desirable to improve the atom- and step-economy as well as high selectivity. We envisioned a new and powerful method to address this need.
In our previous work, we have developed a synthetic method for the unsymmetrical pyridine-bridged pincer-type imidazolium salts,[18] which have shown to be effective organocatalysts.[19] Moreover, metal-based catalysts[20] by coordinating with unsymmetrical ligands have been successfully used in the cycloaddition of epoxides with CO_2 and the Suzuki coupling reaction.[21] During the preparing of the metal-catalysts, we discovered that the benzimidazole salts can hydrolyze to form the ring opened products (Scheme 3, the first step),[21] this result was met with other groups'.[22] Recently, direct C−H bond activation have emerged as an efficient and powerful strategy toward complex molecules construction with high atom- and step-economy.[23] Success in C−H bond activation made it possible based on the ring opened hydrolysis products to seven-membered diazepine ring, which established a powerful new synthetic tool at the C3 position of pyridine ring (Scheme 3, the second step). In this article, we report a straightforward and atom-economical strategy for construction of pyrido-benzodiazepine

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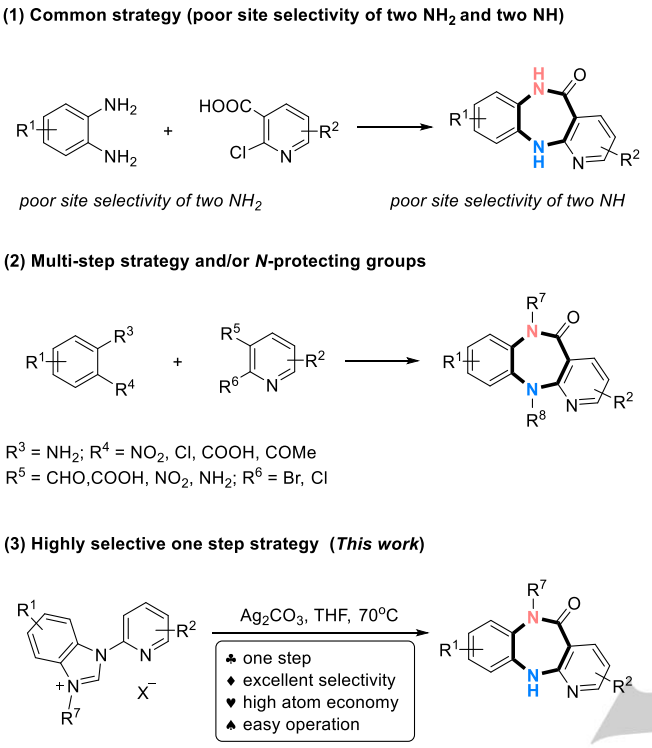
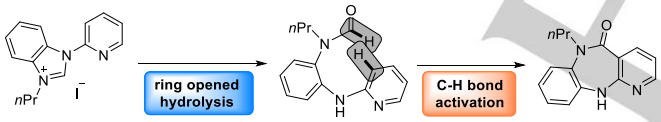
derivatives through continuous ring-opening hydrolysis of benzimidazole salts and intramolecular C−H bond activation.



Scheme 2. Strategies for the construction of pyrido-benzodiazepine.

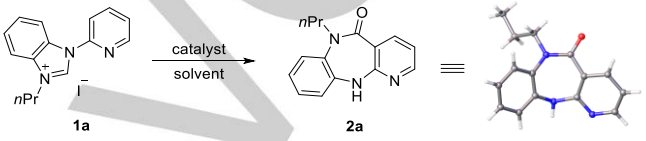


Scheme 3. Cut and sew strategy for the construction of pyrido-benzodiazepine derivatives.

Results and Discussion

In order to identify a suitable catalyst system, as well as suitable reaction conditions, we started our investigation to synthesize benzodiazepine ring derivatives *via* continuous ring-opening hydrolysis and intramolecular C−H bond activation of benzimidazole salts **1a**. Silver salts, including Ag_2O, AgF, $AgPF_6$, $AgNO_3$, and Ag_2CO_3 were screened, and Ag_2CO_3 showed the best performance (Table 1, entry 5). Ag_2O was also able to promote this reaction (Table 1, entry 1); however, it displayed much lower performance than Ag_2CO_3. Other silver salts hardly showed any activity (Table 1, entries 2-4). After screening the solvents (see Table S1 in the Supporting Information), it was found that Ag_2CO_3 combined with THF was a high effective system for this reaction. As expected, increasing reaction temperature was favorable toward product formation. The yields of product increased from 63% to 76% when reaction temperature increased from 60 ºC to 70 ºC (Table 1, entries 5 vs 6). The loading amount of Ag_2CO_3 is crucial for the transformation and a 3 equiv. Ag_2CO_3 exhibits the best result (Table 1, entries 6-9). It is noteworthy that the operation procedure has an obvious effect on the reaction transformation (Table 1, entries 6 vs 11). **1a** and Ag_2CO_3 stirred in THF at room temperature for 2 h is required to acquire high conversion. After this, heating reaction mixtures to reflux for 22 h afforded the desired product **2a**.

Table 1. Optimization of reaction conditions.[a]



Entry	Silver salts (mmol)	T (°C)	Time (h)	Yield (%)
1	Ag_2O (1.5)	60	2+22[b]	24
2	AgF (1.5)	60	2+22[b]	NR
3	$AgPF_6$ (1.5)	60	2+22[b]	NR
4	$AgNO_3$ (1.5)	60	2+22[b]	NR
5	Ag_2CO_3 (1.5)	60	2+22[b]	63
6	Ag_2CO_3 (1.5)	70	2+22[b]	76
7	Ag_2CO_3 (2.0)	70	2+22[b]	79
8	Ag_2CO_3 (1.0)	70	2+22[b]	59
9	Ag_2CO_3 (0.5)	70	2+22[b]	21
10	Ag_2CO_3 (1.5)	rt	2+22[b]	NR
11	Ag_2CO_3 (1.5)	70	24[c]	54

[a] Reaction conditions: benzimidazole iodine salt **1a** (0.5 mmol), silver salt (1.5 mmol), THF (tetrahydrofuran, 2 ml). [b] the reaction was first stirred for 2 h at room temperature and then heated to reflux (60 or 70 °C) for 22 h. [c] The reaction was directly heated to reflux for 24 h.

With the optimized reaction conditions in hand, the scope of the benzimidazole iodine salt for synthesis of the benzodiazepine ring compounds was investigated in Table 2. The effect of substituents of quaternary ammonium cations were first investigated under the optimized reaction conditions. The aliphatic substituents of quaternary ammonium salts, such as methyl, *n*-propyl, *i*-propyl, *n*-butyl, benzyl, phenylpropyl, and allyl group, proceeded smoothly to generate the desired benzodiazepine ring products in moderate to good yields (Table 2, **2a**-**g**). Single crystal X-ray diffraction analysis of **2b** and **2f** were consistent with the desired products

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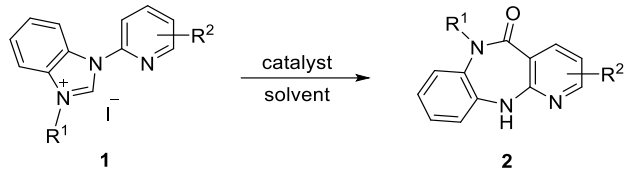
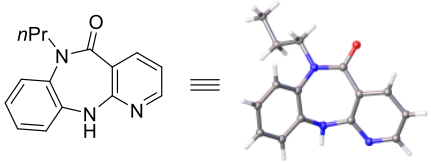
structure, confirming the predicted structures of the pyrido-benzodiazepine products. The electron nature of substituents at the *ortho*-position to the pyridine ring was explored using *N*-propyl substituted substrates. It was found that various substituents at pyridine ring both electron-neutral and electron-donating group, such as fluoro, bromo, chloro, cyano, acetyl, trifluoromethyl, methyl, pyrazolyl, indazolyl, methoxy, and morpholino group, were suitable for construction of benzodiazepine ring derivatives through continuous ring-opening hydrolysis of benzimidazole salts and intramolecular C−H bond activation, giving the desired products in moderate to excellent yields (Table 2, **2h**-**r**). The molecular structure of **2p** was confirmed by X-ray crystallography. This reaction system tolerated different substituents at *meta*- and *para*-position to the pyridine ring. This affords the desired products with 65-87% yield (Table 2, **2s**-**y**).

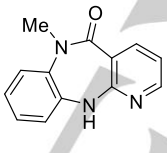
Table 2. Scope of substrates.[a]

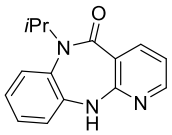


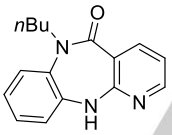
1 **2**

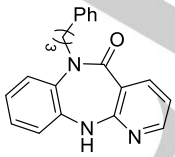

2a, 76%

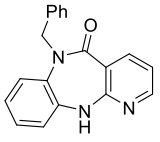
X-ray for **2a**

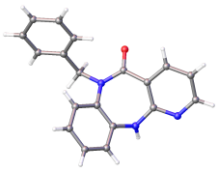

2b, 70%

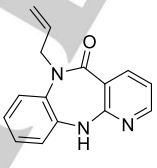

2c, 71%

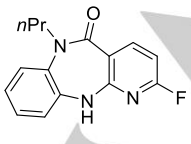

2d, 73%

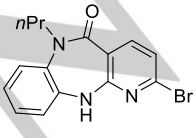

2e, 61%

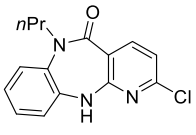

2f, 62%

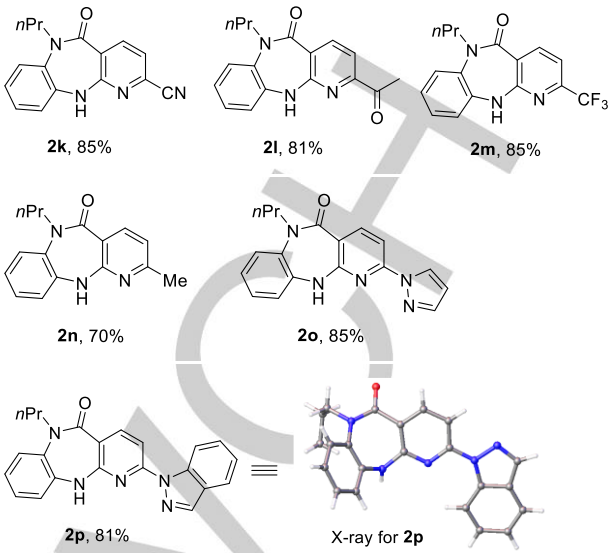

X-ray for **2f**

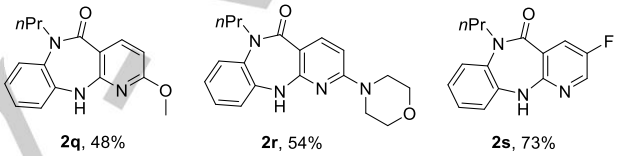

2g, 65%

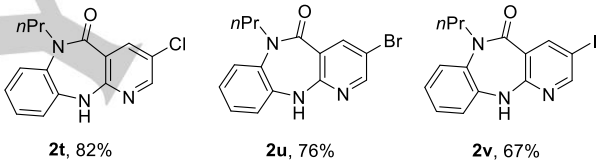

2h, 59%

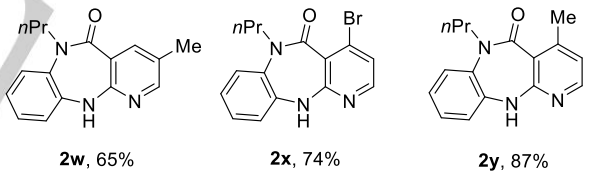

2i, 70%


2j, 74%









[a] Reaction conditions: benzimidazole iodine salt **1a** (0.5 mmol), Ag_2CO_3 (1.5 mmol), THF (tetrahydrofuran, 2 ml), the reaction was first stirred for 2 h at room temperature and then heated to reflux (70 °C) for 22 h.

Encouraged by these promising results aforementioned, we next proceeded to evaluate *N*-heteroaryl substituted substrates (Table 3). As showed in Table 3, two *N*-heteroaryl substituted quaternary ammonium salts, such as quinoline and pyrazine, could smoothly afford the pyrido-benzodiazepine products in a high yield of 82% (Table 3, **3a**) and 71% (Table 3, **3b**), respectively. The effect of substituents of benzimidazole were also explored under the optimized reaction conditions. It was found that benzimidazole with a wide range of functional groups such as methyl, ester, nitro, bromo, chloro, and methoxy were tolerated and moderate to good yields of products were obtained (Table 3, **3c**-**k**). When substrates such as substituents at 8- or 9-position to benzene ring were employed, the phenomenon of the existence of isomers is usually observed. It was found that the electronic effect of substituents at 8- or 9-position to benzene ring for the selectivity of products was

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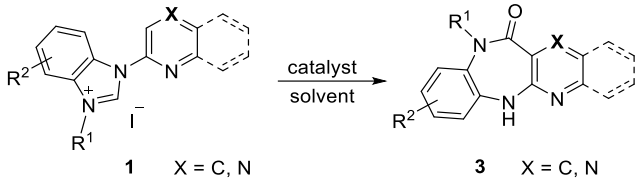
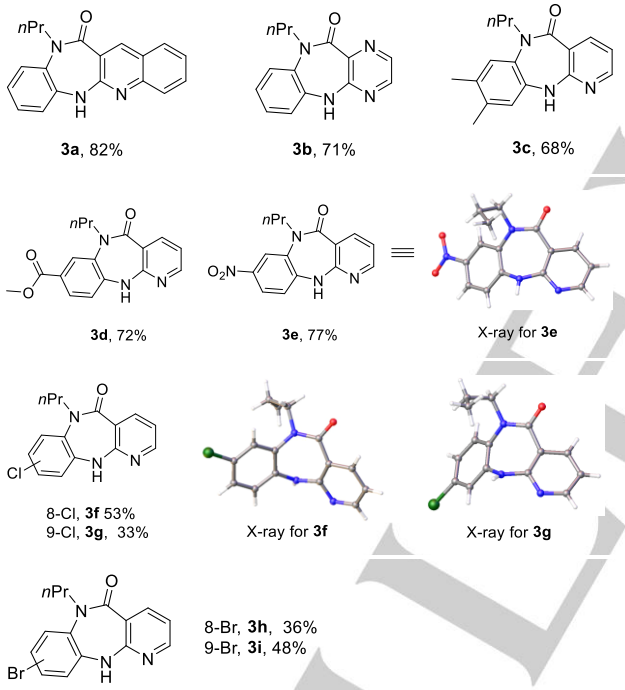
shown to be remarkable. In the presence of electron-withdrawing group such as ester and nitro group, the benzodiazepine ring products **3d** and **3e** were isolated in good yields with the exclusive regioselectivity at 8-position to benzene ring. Unexpectedly, substrates of halogenated substituents such as bromo and chloro group, produced **3f-i** in 8- or 9-substituted mixture products. Delightedly, the resulting 8- or 9-substituted mixture products were easy to separate and gave 8- and 9-halogenated products, respectively. The structures of **3h** (chloro group at 8-position) and **3i** (chloro group at 9-position) were confirmed by the X-ray crystallography.

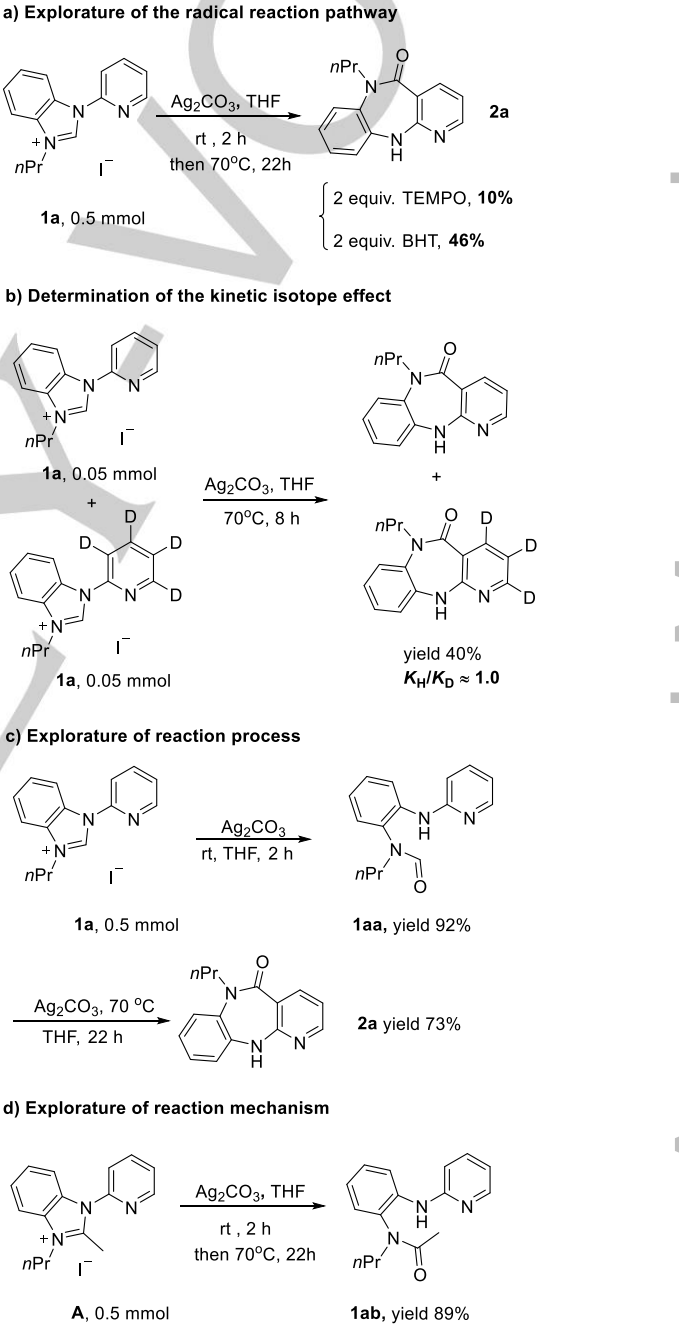
Table 3. Scope of nitrogen heterocycles.[a]





[a] Reaction conditions: benzimidazole iodine salt **1a** (0.5 mmol), Ag_2CO_3 (1.5 mmol), THF (tetrahydrofuran, 2 ml), the reaction was first stirred for 2 h at room temperature and then heated to reflux (70 °C) for 22 h.

The aforementioned successful results prompted us to further explore the reaction mechanism by the radical inhibition and kinetic isotope effect (KIE) experiments. First, the radical inhibition experiments revealed that the addition of 2,2,6,6-tetramethylpiperidine-*N*-oxyl (TEMPO, 2.0 equiv.) and butylated hydroxytoluene (BHT, 2.0 equiv.) as a radical quencher, respectively, partially inhibits the reaction (Scheme 4, a). This result indicates that the radical pathway may be not involved in this transformation. As indicated in Scheme 4, no kinetic isotope effect (KIE ≈ 1) was obtained, suggesting that C-H bond cleavage at C-3 position to pyridine ring is not the rate-limiting step, (Scheme 4, b), which agrees with the calculated results (Figure 1). Control experiments (Scheme 4, c) indicates that a ring-opening product is formed *via* hydrolysis of benzimidazole salts, which further occurred an intramolecular C−H bond activation, resulting in the benzodiazepine ring product **2a**.



Scheme 4. Control experiments for reaction mechanism.

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In order to determine whether the transformation undergoes C-H activation, we have designed a control experiment (Scheme 4, d). It is found that when methyl is introduced into C2 of benzimidazole ring (**A**), the reaction can still proceed to give the ring opening product but no benzodiazepine ring product was formed. The results suggest that C-H activation is not involving in the reaction process.

As shown in Figure 1, the DFT calculations were performed for explore the possible pathway associated with the structural transformation from **I** to **V**. The first step is the water-assisted proton transfer, which coupled with the C-N bond breaking for the transformation from intermediate **I** to **II** via transition state $\mathbf{TS_{I\text{-}II}}$. The next step is the deprotonation process of aldehyde by Ag_2CO_3 to form **III** via $\mathbf{TS_{II\text{-}III}}$. In the third step, it is the other deprotonation process of pyridine ring by the other Ag_2CO_3 via transition state $\mathbf{TS_{III\text{-}IV}}$. The last step is the C–C bond formation step via transition state $\mathbf{TS_{IV\text{-}V}}$. The calculated energy barriers are 31.4, 28.5, 28.5, and 33.7 kcal/mol via transition states $\mathbf{TS_{I\text{-}II}}$, $\mathbf{TS_{II\text{-}III}}$, $\mathbf{TS_{III\text{-}IV}}$, and $\mathbf{TS_{IV\text{-}V}}$, indicating that the reaction can occur under the heating condition.

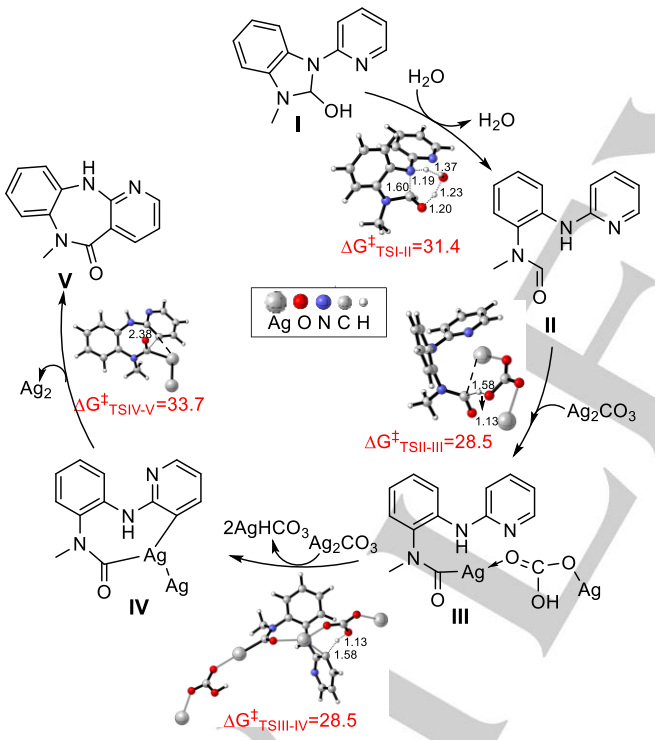
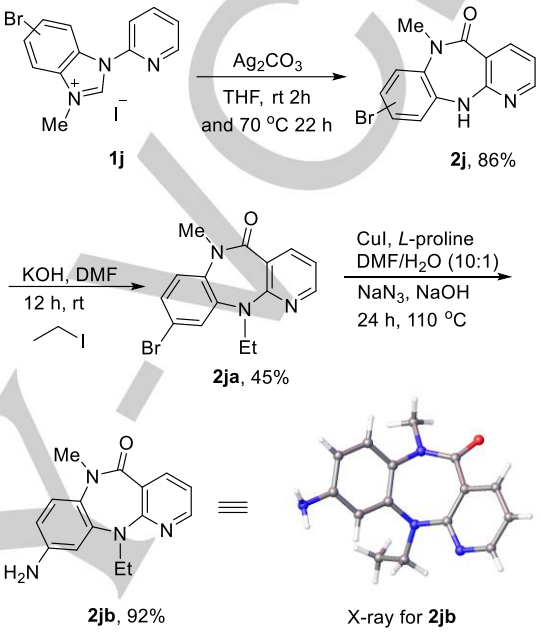


Figure 1. The possible reaction progress confirmed by DFT calculations (distance in angstrom).

In traditional method, two NH group of the pyrido-benzodiazepine generally suffer from poor site selectivity or the multistep procedures (Scheme 2, both pathway 1 and 2) when they are functionalized. The synthetic utility of this transformation in comparation with the common strategy was next explored. Further transformation of the obtained *N*-methyl substituted the pyrido-benzodiazepine product **2j** gave an unsymmetrical *N*-methyl and *N'*-ethyl substituted pyrido-benzodiazepine **2ja** (Scheme 5). Bromo group of benzene ring further reacts with NaN_3 in the presence of CuI as a catalyst to delivered the NH_2 functionalized pyrido-benzodiazepine product **2jb**. The structure of resulting product **2jb** was confirmed by the X-ray crystallography (Scheme 5).



Scheme 5. Functionalization of the pyrido-benzodiazepine.

Conclusion

In conclusion, a new method for one-step synthesis of the pyrido-benzodiazepine backbones and its analogues based on a successive ring-opening hydrolysis of benzimidazole salts and intramolecular C−H bond activation is reported. The procedure featured broad substrate scope, together with excellent functional group tolerance, affording products in moderate to excellent yields. One significant and advantageous feature of this new strategy lies in easy operation (without removal of moisture and oxygen), atom- and step-economy. The experiments using radical-scavenging reagents indicated that a radical pathway may be not involved in this reaction transformation. The kinetic isotope effect (KIE) experiments suggested that C-H bond cleavage at C-3 position to pyridine ring was not the rate-limiting step. The control experiments and density functional theory calculations (DFT) were performed to support a possible reaction process. We believe this practical and convenient synthetic procedure will find promising uses in constructing pharmaceutically important pyrido-benzodiazepine.

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Computational Methods

The DFT calculations were performed using the Gaussian 16 program.[24] All structures were fully optimized at the B3LYP[25]/DGDZVP level in THF solvent using the integral equation formalism polarizable continuum model (IEF-PCM).[26] Then, frequency calculations at the same level of theory were carried out to identify all of the stationary points as minima (zero imaginary frequency) or transition state (only one frequency), and to provide free energies.

Acknowledgements

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Conflict of interest

The authors declare no conflict of interest.

Keywords: C-H bond activation • Silver • Cascade reaction • Seven-membered ring • Benzodiazepine

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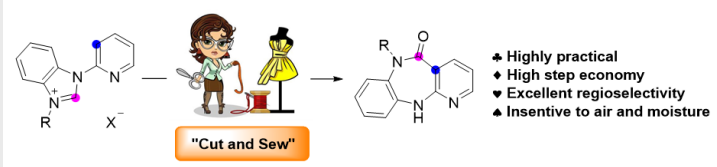

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