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Rhodium-catalyzed reactions of 3-diazoindolin-2-imines with enamines and their extensions towards 5*H*-pyrazino[2,3-*b*]indoles

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ABSTRACT

The rhodium-catalyzed reactions of 3-diazoindolin-2-imines with β-enamino esters furnished 2,3-diaminoindoles in excellent yields with wide functional group tolerance. The synthesized 2,3-diaminoindoles could be converted into 5*H*-pyrazino [2,3-*b*]indoles via a sequential dehydrogenation/6π-ERC/aromatization process.

1. Introduction

Carbazoles and aza-carbazoles are important classes of heterocycles in medicinal chemistry and functional material science due to their wide range of biological activities[1] and optical properties.[2] For example, ellipticine, B-220, and glycobrinen are anticancer or anti-viral agents,[3] carvedilol has been clinically used to treat congestive heart failure, and 2,6-2C$_Z$BN is a thermally activated delayed fluorescence material (Fig. 1).[4] Among of these heterocycles, 6*H*-indolo [2,3-*b*]quinoxalines are attracted much attention duo to their potential applications in medicinal chemistry and material science. The published methods for the construction of 5*H*-pyrazino [2,3-*b*]indole ring include the thermal cyclization of pyrazinylhydrazone followed by oxidative dehydrogenation.[5] the condensation of the in situ generated 2,3-diaminoindole with α-diketone,[6] the condensation of indoline-2,3-dione with benzene-1,2-diamine.[7] More recently, we reported a novel synthesis of 5*H*-pyrazino [2,3-*b*]indoles via rhodium-catalyzed reaction between 3-diazoindolin-2-imines and 2*H*-azirines, followed by treatment with base (Scheme 1, Our Previous Work). The resulting 5*H*-pyrazino [2,3-*b*]indoles present strong photoluminecence in solutions, in powders, and in films.[8] Encouraged by these results and our successes on the development of new diazo reagents[9] and their synthetic applications as metal carbene precursors for,[8–10] we herein report another feasible access to 5*H*-pyrazino [2,3-*b*]indoles, which is triggered by a rhodium-catalyzed N–H insertion of 3-diazoindolin-2-imines with enamines (Scheme 1, This Work).

2. Results and discussion

In our previous works, we successfully obtained 2,3-diaminoindole derivatives from 3-diazoindolin-2-imines via the N-H insertion reaction of Rh-carbene with secondary amines.[9b] However, when primary amine (e.g. aniline, ethanamine and ethane-1,2-diamine), benzenesulfonamide, and benzamide were used, N-H insertion did not occur or very complex mixture products were observed. Based on this result and inspired by Lee's work on the Rh(II)-catalyzed cascade reaction of N-sulfonyl-1,2,3-triazoles with ambiphilic β-enamino esters, which afforded 2,5-dihydro-1*H*-imidazoles (3-imidazolines),[11] we rechecked the possibility of N-H insertion of β-enamino esters to the metal carbene in situ generated from 3-diazoindolin-2-imines. In our primary experiment, reaction of 3-diazo-indolin-2-imine **1a** and (Z)-3-amino-3-phenylacrylate (**2a**) was selected as the modal reaction (Table 1).

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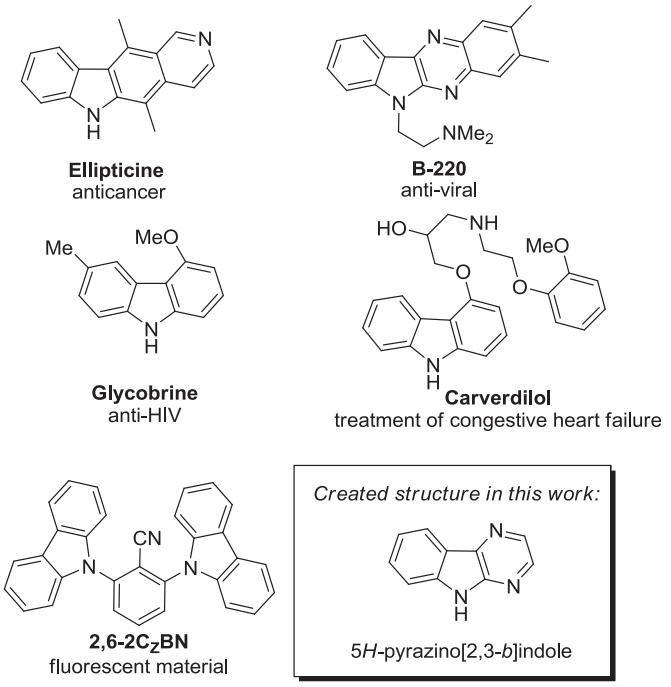
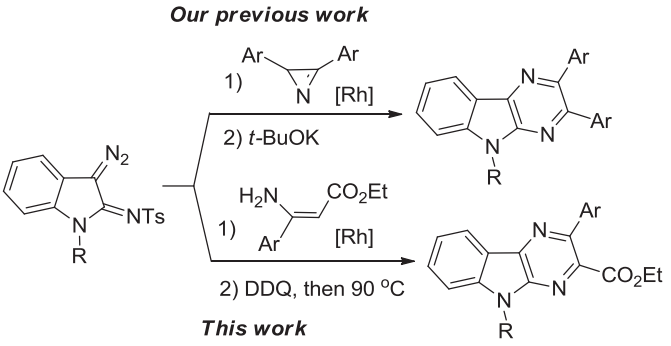


Fig. 1. Representative carbazoles and aza-carbazoles with biological activity or optical property.

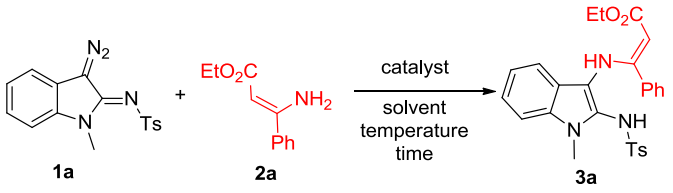


Scheme 1. Previous synthesis of 5*H*-pyrazino [2,3-*b*]indoles and this work.

When the reaction was performed using $Rh_2(Oct)_4$ (2 mol %) as catalyst in $CHCl_3$ 60 °C for 2 h, a N–H insertion product **3a** was obtained in 78% isolated yield (Table 1, entry 1). The structure of **3a** was confirmed by its single crystal analysis.[12] The *Z*-form configuration of C=C bond in β-enamino ester group was formed due to the intramolecular hydrogen bonding. Delighted by this result, we then screened the reaction conditions, including solvent (e.g., dichloroethane and toluene) (Table 1, entries 2 and 3), catalyst (e.g., $Rh_2(OAc)_4$, Rh_2 (R-DOSP)$_4$, $[(CF_3COO)_2Rh]_2$, CuOTf·1/2C_6H_6, and $Cu(OTf)_2$) (Table 1, entries 4–9), reaction temperature (Table 1, entries 10 and 11), and reaction time (Table 1, entries 12 and 13). 1,2-Dichloroethane (DCE) was determined to be the optimal solvent, while $Rh_2(Oct)_4$ was the best rhodium catalyst (Table 1, entries 2, 4–6). The optimal reaction temperature and time were determined to be 60 °C and 2 h, respectively (Table 1, entries 2, 9–13).

We then investigated the substrate diversity using the optimal reaction conditions (Scheme 2). The substituent on N1-position of 3-diazoindolin-2-imine could be altered from methyl (**1a**) to ethyl (**1b**), isopropyl (**1c**), allyl (**1d**), and benzyl (**1e**). Thus, compounds

Table 1
Screening of the reaction conditions.[a]



Entry	Catalyst	Solvent	Temp (°C)	Time (h)	Yield (%)[b]
1	$Rh_2(Oct)_4$	$CHCl_3$	60	2	78
2	$Rh_2(Oct)_4$	DCE	60	2	91
3	$Rh_2(Oct)_4$	PhMe	60	2	86
4	$Rh_2(OAc)_4$	DCE	60	2	53
5	Rh_2 (R-DOSP)$_4$	DCE	60	2	trace
6	$[(CF_3COO)_2Rh]_2$	DCE	60	2	trace
7	CuOTf·1/2C_6H_6	DCE	60	2	43
8	$Cu(OTf)_2$	DCE	60	2	61
9	None	DCE	60	2	N.R
10	$Rh_2(Oct)_4$	DCE	40	2	84
11	$Rh_2(Oct)_4$	DCE	80	2	76
12	$Rh_2(Oct)_4$	DCE	60	1	80
13	$Rh_2(Oct)_4$	DCE	60	3	82

[a] Reaction conditions: **1a** (0.2 mmol), **2a** (0.24 mmol), catalyst (0.004 mmol), solvent (2 mL).
[b] Isolated yield.

3a-e were prepared in yields ranging from 84% to 91%. In the case where **3d** was produced, the double bond of allyl did not participate in the reaction and survived after the reaction finished. The substituent on the 5-position of 3-diazoindolin-2-imine could be either electron-withdrawing (**3f**, 82% yield) or electron-donating group (**3g**, 84% yield). The sulfonyl group could either be other arenesulfonyl (products **3h-j,** 87–95% yields) or methanesulfonyl (product **3k,** 92% yield). Finally, we tested the scope of the β-enamino esters **2**. The substituent on the phenyl ring of (*Z*)-3-amino-3-arylacrylates **2** could be *p*-, *m*-, and *o*-methyl (**3l-n**), *p*-methoxy (product **3o**), and *p*-nitro (**3p**). In these cases, **3l-p** were prepared in excellent yields. Finally, 7-methyl-substituted 3-diazoindolin-2-imine and 2-methyl-substituted 3-amino-3-phenylacrylate were also examined and they provided the corresponding products **3q** and **3r** in 87% and 80% yields, respectively.

By treating the synthesized compounds **3** with DDQ in dichloromethane at room temperature for half hour, the corresponding oxidation products **4a-f** were obtained in quantitative yields (Scheme 3). Further treatment of **4a-f** in toluene at 90 °C for 36 h resulted in the cyclized products **5a-f** in 45%–78% yields. It was noticeable that the desulfonylation occurred in this transformation.

In order to understand the mechanism, a controlled reaction was conducted. When the cyclization was conducted in toluene at 80 °C for 6 h, compound **6** was isolated in 10% yield. Further heating **6** in toluene at 90 °C for 42 h, **5a** was obtained in 95% yield. Based on the above observations, we postulated a working mechanism for the formation of **3**, **4**, and **5** (Scheme 4). At the beginning, α-imino rhodium carbene **A** was formed by reaction between **1a** and rhodium catalyst. Next, the rhodium carbene reacted with enamine **2a** lead to N-H insertion Subsequently, 1,3-Rh migration and Rh-H exchange formed, **3a** as a sole product. When DDQ was added as the oxidant, dehydrogenation occurred and gave rise to a larger conjugated system, termed aza-triene **4a**, which was a good candidate for electron ring closure (6π-ERC). Thus, 4,5-dihydro-3*H*-pyrazino [2,3-*b*]indole **6** was obtained. Finally, aromatization occurred after the elimination of toluenesulfinic acid, leading to the