Synthesis of Polycyclic Dihydroindoles by Selective Decomposition of Bis(1,2,3-triazoles) Mediated by Rhodium Catalysis

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Abstract: We report the selective decomposition of bis(1,2,3-triazoles) under rhodium(II) catalysis. The bis(1,2,3-triazoles) undergo an intramolecular transannulation reaction *via* an azavinylcarbene intermediate, resulting in the formation of polycyclic dihydroindoles containing a fused triazole ring.

Keywords: azavinylcarbenes; click chemistry; rhodium(II) catalysis; triazoles

Substituted indoles are encountered in a vast number of heterocyclic molecules with a wide range of applications ranging from medicinal to material chemistry.^[1] More specifically, 3,4-fused indoles and hapalindole alkaloid analogues are important pharmacophores found in Nature, such as dehydrobufotenine, chanoclavine, lysergic acid, and cyclavine (Figure 1).^[2] Generally, this type of fused indole can be synthesized only *via* multistep procedures.^[2d,3] Therefore, the bio-

logical properties of these types of fused heterocycles remain for the most part unexplored because of the difficulties in obtaining them in sufficient quantities. Hence, the development of atom economic one-step synthetic strategies towards 3,4-fused indoles is highly desirable.

In recent years, azavinylcarbenes derived from *N*-sulfonyl-1,2,3-triazoles have drawn considerable attention in the chemical community as a means towards the synthesis of various heterocycles which are otherwise very difficult to prepare.^[4,5,6] 1,2,3-Triazoles are known to be very stable heterocycles, however they can be decomposed to azavinylcarbenes by using appropriate substituents on the 1,2,3-triazole ring and a transition metal catalyst. In 2007, Gevorgyan was first to point out that 1,2,3-triazoles could be cleaved by transition metal catalysis to azavinylcarbene species, which was further used in various transformation.^[4,5,6] Since then, a vast number of synthetic strategies have been discovered including transannulation, cyclopropanation, dehydrogenative rearrangements, C–H bond insertion, ring expansion, and ylide formation, in which 1-sulfonyl-1,2,3-triazoles have been used as a carbene precursor.^[4,5,6] We have been working on the development of various synthetic strategies towards the synthesis of functionalized 1,2,3-triazoles.^[7] Recently, we have reported a novel methodology towards the synthesis of propargyl-substituted 1,2,3-triazoles, and further functionalization of these triazoles *via* Cu(I)-catalyzed click reactions resulted in the formation of unique N,C-linked bis(1,2,3-triazoles).^[7a]

In 2014 Murakami et al. reported an intramolecular dearomatizing annulation reaction of 4-(3-arylpropyl)-1,2,3-triazoles furnishing dihydroindole skeletons.^[4k] Inspired by this report, we have anticipated that this reaction could be applied to the N,C-linked bis(1,2,3-triazoles) bearing the appropriate substituents (Scheme 1). The bis(1,2,3-triazole) **1a**, has been synthesized from *N*-propargyl-5-phenyltriazole with tosyl azide in the presence of copper(I) thiophene-2-carboxylate (CuTc) catalyst. As we had hoped, our in-

Figure 1. Representative bioactive molecules with a 3,4-fused indole core.

a) previous work: decomposition of triazole into azavinylcarbene

b) this work: selective decomposition of triazole into azavinylcarbene

Scheme 1. Decomposition of triazole into azavinylcarbene.

initial trial with **1a** in the presence of Rh(II) leads to selective decomposition of the 1,4-disubstituted 1,2,3-triazole core, leading to a 3,4-fused dihydroindole **2a** via an intramolecular [3+2]-annulation reaction. To the best of our knowledge, this is the first example of a selective decomposition of bis(1,2,3-triazoles) into azavinylcarbenes in the presence of a rhodium catalyst.

After getting this promising result, we started to optimize this novel annulation reaction (Table 1). Triazole **1a** was treated with a catalytic amount of Rh₂(OAc)₄ in dry DCE at 80 °C under a nitrogen atmosphere, and the desired fused indole **2a** was obtained in 43% yield after 12 h. An increase in yield

was observed when the reaction time was reduced to 4 h. Next, changing the catalyst from Rh₂(OAc)₄ to Rh₂(esp)₂ resulted in a significant increase in yield under the same conditions. Other catalysts, such as Rh₂(oct)₄ used by Murakami et al.,^[4k] Rh₂(Piv)₄, and Rh₂(tpa)₄ gave no better result. It was found that the yield decreased if the reaction was carried out at a lower or a higher temperature than 80 °C. Also, changing the solvent to toluene, CHCl₃ and cyclohexane resulted in slightly lower yields.

With the optimized conditions in hand, we started to investigate the role of the sulfonyl group substituents (Scheme 2). It was found that neither electron-donating or electron-withdrawing groups on the phenylsulfonyl ring had a significant effect on the outcome of the reaction (**2b** and **2c**). Next, the substitution effect on the 5-aryl ring was investigated (Scheme 2). Electron-donating groups such as Me (**2d**) and OMe (**2e**) at the 4-position resulted in slightly lower yields, whereas an electron-withdrawing

Table 1. Optimization of the reaction conditions.^[a]

Entry	Catalyst	Temp. [°C]	Time [h]	Solvent	Yield ^[b] [%]
1	Rh ₂ (OAc) ₄	80	12	DCE	43
2	Rh ₂ (OAc) ₄	80	4	DCE	46
3	Rh ₂ (oct) ₄	80	4	DCE	51
4	Rh ₂ (Piv) ₄	80	4	DCE	63
5	Rh ₂ (tpa) ₄	80	4	DCE	49
6	Rh₂(esp)₂	80	4	DCE	76
7	Rh ₂ (esp) ₂	60	4	DCE	57
8	Rh ₂ (esp) ₂	100	4	DCE	66
9	Rh ₂ (esp) ₂	80	4	toluene	69
10	Rh ₂ (esp) ₂	80	4	CHCl ₃	70
11	Rh ₂ (esp) ₂	80	4	cyclohexane	63

^[a] All reactions were conducted on a 0.26 mmol scale in 4 mL solvent with 5 mol% catalyst under an N₂ atmosphere.

^[b] Isolated yield. Rh₂(tpa)₄=Rh₂(triphenylacetate)₄, Rh₂(esp)₂=bis[rhodium(α,α,α',α'-tetramethyl-1,3-benzene-dipropionic acid)].

Scheme 2. Scope of the dearomatizing *trans* annulation reaction of bis(1,2,3-triazoles). General conditions: **1** (0.23 mmol), and Rh₂(esp)₂ (0.012 mmol), in DCE (4 mL) at 80 °C for 4 h, unless otherwise noted.

group such as F (**2f**) at the *para* position resulted in an increased yield. Similar trends were observed in the case of the *meta* isomers. For instance, *meta*-F (**2h**) and *meta*-CF₃ (**2i**) substrates afforded excellent yields as compared to the *meta*-Me (**2g**) counterpart.

In order to prove the generality of this reaction, in addition to the transannulation reaction onto different substituted phenyl groups, the use of heterocyclic dibenzofuran was also investigated (Scheme 3). Substrate **1k** underwent Rh(II)-catalyzed intramolecular cyclization to give the corresponding polyheterocyclic product **2k** in good yield.

Scheme 3. Use of benzofuran in the transannulation reaction towards **2k**.

3,4-Fused indole alkaloid analogues are interesting pharmacophores which could be accessible *via* oxidative aromatization of dihydroindole. Similar to Murakami et al.^[4k] the oxidation reaction of 3,4-dihydroindole **2a** was carried out with MnO_2 . This afforded the triazole-fused alkaloid analogue **3** in excellent yield (Scheme 4).

Scheme 4. Formation of fused indole derivatives.

The synthetic utility of the Rh(II)-catalyzed selective 1,2,3-triazole decomposition and annulation reaction was further exemplified by a one-pot synthesis of 3,4-fused dihydroindole **2a** starting from propargyl triazole **4** in moderate yield (Scheme 5). Thus, in this way the interesting 1,2,3-triazole-derived (dihydro)indole alkaloid analogues are accessible in a few reaction steps.

A sequential one-pot synthesis of fused indole **3** was also carried out starting from bis(1,2,3-triazoles)

Scheme 5. One-pot procedure starting from propargyl triazoles.

1a. A mixture of bis(1,2,3-triazole) **1a** and $\text{Rh}_2(\text{esp})_2$ was heated at 80 °C in DCE for 4 h to form the dihydroindole. Subsequently, MnO_2 was added to the same reaction vessel, and the mixture was further stirred at 80 °C for 24 h to afford the fused indole of bis(1,2,3-triazole) **3** in good yield. Thus the sequential one-pot reaction provides an easy access to triazole-fused indole **3** in good yield (Scheme 6).

Scheme 6. One-pot procedure to access triazole-fused indoles from bis(1,2,3-triazoles).

A reaction mechanism is postulated on the basis of the previous literature reports^[4–6] (Scheme 7). Triazole **1a** is in equilibrium with ring-chain tautomer α -diazo imine **I**, which subsequently reacts with Rh(II) affording α -imino rhodium carbene complex **II** and releases molecular dinitrogen. Then, intramolecular nucleophilic attack occurs of the phenyl at the electrophilic carbene center in a 6-*exo* mode to generate zwitterionic species **III**. In a final step, the anionic rhodium of **III** undergoes elimination which drives the final cyclization step, leading to final product **2a** and regenerating the Rh(II)-catalytic species.

In conclusion, we have disclosed an unprecedented selective decomposition of bis(1,2,3-triazoles) by a Rh(II)-catalyzed [3+2]-intramolecular annulation reaction which leads to the formation of 3,4-fused indoles. Extension of this protocol to heterocycles led to interesting polyfused 1,2,3-triazole derivatives. This protocol presents a simple, one-step, and atom economic efficient method for the synthesis of 1,2,3-triazole-fused dihydroindoles and indoles, which could so far not be synthesized by other means. Further applications of these products in medicinal chemistry are in progress and will be reported in due course.

Scheme 7. Proposed reaction mechanism.

Experimental Section

General Procedure for the Preparation of Bis-triazoles

A flame-dried tube was charged with the appropriate propargyl triazole (0.66 mmol), CuTc (0.06 mmol), and tosyl azide (0.73 mmol) in dry toluene (2 mL) under an N₂ atmosphere. The resultant mixture was heated at 60 °C for 3 h. After consumption of the starting material as apparent from TLC analysis, the crude reaction mixture was concentrated under vacuum, and the product was isolated by flash column chromatography (EtOAc:heptane 1:1) to afford the pure product.

Typical Procedure for the Oxidative Aromatization Reaction

A flame-dried reaction tube was charged with dihydroindole **2a** (100 mg, 0.284 mmol) and MnO₂ (123 mg, 1.419 mmol) in DCE (2 mL). The reaction mixture was then heated at 80 °C for 24 h. After the completion of the reaction, the solvent was evaporated under vacuum. The crude reaction mixture was then directly purified by flash column chromatography (ACN: DCM 1:20) to afford fused indole **4** as an off-white solid; yield: 79 mg (89%).

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